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(54) Title: ALIPHATIC AMINE SUBSTITUTED PIPERIDYL DIARYL PYRROLE DERIVATIVES AS ANTIPROTOZOAL
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(57) Abstract: Trisubstituted pyrroles are antiprotozoal agents useful in the treatment and prevention of protozoal diseases in human
and animals, including the control of coccidiosis in poultry.

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TITLE OF THE INVENTION

ALIPHATIC AMINE SUBSTITUTED PIPERIDYL DIARYL PYRROLE
DERIVATIVES AS ANTIPROTOZOAL AGENTS

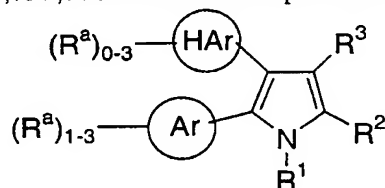
5 BACKGROUND OF THE INVENTION

Parasitic protozoa are responsible for a wide variety of infections in man and animals. Many of the diseases are life threatening to the host and cause considerable economic loss in animal husbandry. For example, malaria remains a significant health threat to humans despite massive international attempts to eradicate the disease; trypanosomiasis such as Chagas disease caused by *Trypanosoma cruzi* and African sleeping sickness caused by *T. brucei* are not uncommon in Africa and South America; and opportunistic infections in immunocompromised hosts caused by *Pneumocystis carinii*, *Toxoplasma gondii*, *Cryptosporidium* sp. are becoming increasingly significant in the developed countries.

15 A protozoal infection of great economic importance is coccidiosis, a widespread disease of domesticated animals produced by infections by protozoa of the genus *Eimeria*. Some of the most significant of *Eimeria* species are those in poultry namely *E. tenella*, *E. acervulina*, *E. necatrix*, *E. brunetti* and *E. maxima*. The disease is responsible for high levels of morbidity and mortality in poultry and can result in extreme economic losses.

20 In some protozoal diseases, such as Chagas disease, there is no satisfactory treatment; in others, drug-resistant strains of the protozoa may develop. Accordingly, there exists a continued need to identify new and effective anti-protozoal drugs.

25 US Patent 5,792,778 discloses compounds of the formula:



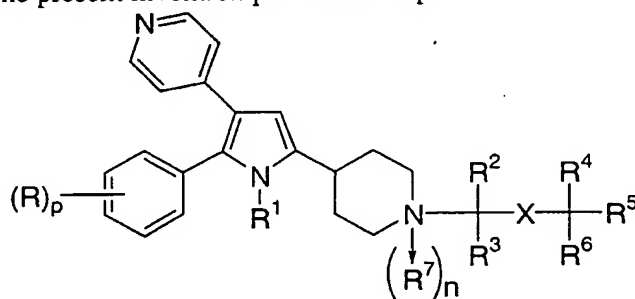
in which HAr may be 4-pyridyl, Ar may be 4-fluorophenyl, R² may be substituted 4-piperidyl and R³ may be hydrogen.

SUMMARY OF THE INVENTION

The instant invention is concerned with diarylpyrrole derivatives which are useful as antiprotozoal agents. Thus, it is an object of this invention to describe such compounds. It is a further object to describe processes for the preparation of such compounds. Another object is to describe methods and compositions which use the compounds as the active ingredient thereof. Further objects will become apparent from reading the following description.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides compounds of formula I:



I

or a physiologically acceptable salt thereof ,
wherein

- 15 n is 0 or 1;
m is 0, 1 or 2;
p is 1, 2 or 3;
X is (1) a bond,
(2) (CR^aR^a)_p,
20 (3) C₃₋₇ cycloalkylene, or
(4) C₃₋₇ cycloalkylidene;
R is halogen
R¹ is (1) hydrogen or
(2) C₁₋₆alkyl;
25 R² and R³ are independently selected from
(1) hydrogen,
(2) C₁₋₆alkyl optionally substituted with OR^b,
(3) C₂₋₆alkenyl,

- (4) C₂₋₆alkynyl,
 (4) phenyl optionally substituted with OR^b,
 (5) benzyl optionally substituted with OR^b,
 (6) CO₂R^b; or
- 5 R² and R³ together represent oxo;
 when X is a bond or (CR^aR^a)_p, R² and R⁴ taken together complete a 4- to 7-
 membered non-aromatic ring containing N-R^f optionally substituted with 1 to 3
 groups independently selected from oxo and R^d; or
 when X is a bond or (CR^aR^a)_p, R² and R⁵ taken together complete a 4- to 7-
 10 membered non-aromatic ring containing 0 to 2 heteroatoms independently selected
 from N-R^f, O and S(O)_m, said ring being optionally substituted with 1 to 5 groups
 independently selected from oxo, OR^b, CH₂OR^b, and C₁₋₆alkyl;
- R⁴ is
- 15 (1) NR^bR^b,
 (2) NR^bC(O)R^b,
 (3) NR^bC(O)OR^b,
 (4) NR^bC(O)NR^bR^b,
 (5) NR^bSO₂R^b,
 (6) NR^bC(=NR^b)NR^bR^b,
 (7) CONR^bR^b; or
- 20 R⁴, R⁵ and the carbon atoms to which they are attached form a 3- to 7-membered
 non-aromatic ring containing N-R^f, optionally containing an additional heteroatom
 selected from O, S(O)_m and N-R^f, and said ring being optionally substituted with 1 to
 3 groups selected from oxo and R^d;
- R⁵ and R⁶ are independently selected from
- 25 (1) hydrogen,
 (2) C₁₋₁₂alkyl,
 (3) C₂₋₁₂alkenyl,
 (4) C₂₋₁₂alkynyl,
 (5) C₃₋₇cycloalkyl-(C₁₋₆alkyl)_n,
 30 (6) heterocyclyl-(C₁₋₆alkyl)_n,
 (7) aryl-(C₁₋₆alkyl)_n,
 (8) heteroaryl-(C₁₋₆alkyl)_n,

wherein alkyl, alkenyl and alkynyl are optionally substituted with 1 to 5 groups independently selected from R^c , cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted with 1 to 3 groups independently selected from R^d , or R^5 , R^6 and the carbon atoms to which they are attached form a 3- to 7-membered non-aromatic carbocyclic ring, optionally substituted with 1 to 3 groups selected from oxo and R^d ; or when X is $(CR^aR^a)_p$, R^5 and any one of the R^a may together complete a 3- to 7-membered non-aromatic carbocyclic ring; or R^5 and R^6 together represent oxo;

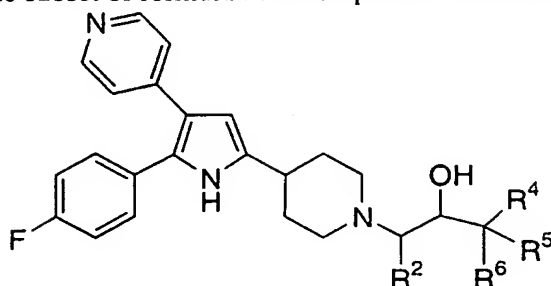
- 10 R^7 is (1) O or
(2) methyl;
 R^a is (1) hydrogen
(2) C_{1-6} alkyl
(3) OR^b ;
- 15 R^b is (1) a group selected from R^5 , or
two R^b groups together with the nitrogen atom to which they are attached form a 3- to 7-membered saturated, unsaturated or aromatic ring optionally containing an additional heteroatom selected from O, $S(O)_m$, N and $N-R^f$, said ring being optionally benzo-fused and optionally substituted with 1 to 3 groups selected from oxo and R^d ;
- 20 R^c is (1) $NReRe$,
(2) $NRgC(O)OR^e$,
(3) $NRgC(O)Re$,
(4) $NRg(C)ONReRe$,
(5) $NRgSO_2Re$,
25 (6) halogen,
(7) $S(O)_mRe$,
(8) OR^e ,
(9) $OC(O)NReRe$,
(10) $OC(O)OR^e$,
30 (11) $OC(O)Re$,
(12) OSO_2Re
(13) OCF_3 ,
(14) CF_3 ,
(15) $C(O)OR^e$,
35 (16) $C(O)Re$,

- (17) oxo,
 (18) N₃,
 (19) CN,
 (20) NO₂, or
 (21) P(O)(OR^e)₂;
- 5 R^d is (1) C₁₋₆alkyl optionally substituted with 1 to 5 groups selected from R^c,
 (2) a group selected from R^c,
 (3) aryl optionally substituted with 1 to 5 groups selected from R^c,
 10 or
 (4) heteroaryl optionally substituted with 1 to 5 groups selected from R^c;
- R^e is (1) hydrogen,
 (2) C₁₋₁₂alkyl,
 15 (3) C₂₋₁₂alkenyl,
 (4) C₂₋₁₂alkynyl,
 (3) C₃₋₇cycloalkyl-(C₁₋₆alkyl)_n,
 (4) aryl(C₁₋₆alkyl)_n,
 (5) heteroaryl(C₁₋₆alkyl)_n,
- 20 wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heteroaryl are optionally substituted with 1 or 2 groups selected from hydroxy and C₁₋₃alkoxy; or two R^e groups together with the nitrogen atom to which they are attached form a 3- to 7-membered ring optionally containing an additional heteroatom selected from O, S or N-R^g;
- 25 R^f is (1) R^e,
 (2) C(O)R^e,
 (3) C(O)OR^e,
 (4) C(O)NR^eR^e, or
 (5) SO₂R^e;
- 30 R^g is (1) H,
 (2) C₁₋₆alkyl, or
 (3) aryl(C₁₋₆alkyl);

with the proviso that when R⁴ is amino or t-butyloxycarbonyl amino, R¹, R⁵ and R⁶ are each hydrogen, and X is a bond, then R² + R³ is not oxo.

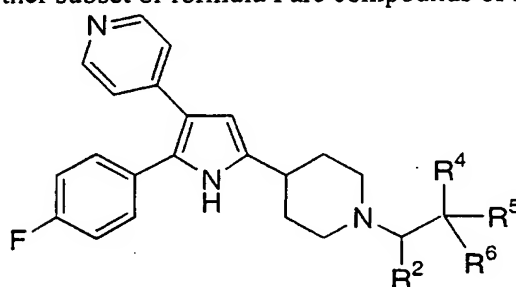
35 In one subset of formula I X is CH(OH) or CH₂.

In one subset of formula I are compounds of formula Ia:



Ia

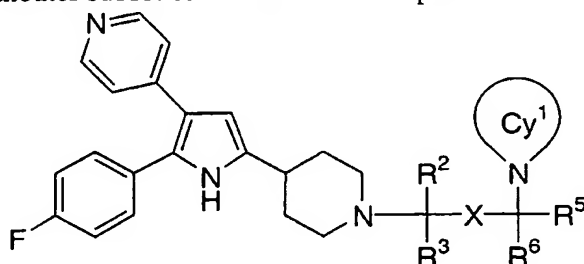
In another subset of formula I are compounds of formula Ib:



Ib

In one embodiment of formula Ib one of R⁵ or R⁶ is other than hydrogen. In another embodiment R² and R⁴ taken together complete a 4- to 7-membered non-aromatic ring containing N-R^f optionally substituted with 1 to 3 groups independently selected from oxo and R^d. In another embodiment R⁵, R⁶ and the carbon atoms to which they are attached form a 3- to 7-membered non-aromatic carbocyclic ring, optionally substituted with 1 to 3 groups selected from oxo and R^d.

In another subset of formula I are compounds of formula Ic:

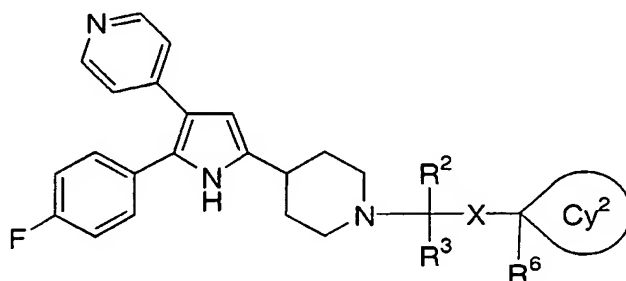


Ic

wherein Cy¹ is a 3- to 7-membered saturated, unsaturated or aromatic ring optionally containing an additional heteroatom selected from O, S(O)_m, N and N-R^f, said ring

being optionally benzo-fused and optionally substituted with 1 to 3 groups selected from oxo and R^d . In one embodiment of formula Ic Cy^1 is a 4- to 6-membered saturated ring optionally containing an additional heteroatom selected from O, $S(O)_m$, and $N-R^f$, and optionally substituted with 1 to 3 groups selected from oxo and R^d . In another embodiment of formula Ic, X is a bond or $CH(OH)$. In another embodiment R^2 and R^3 are each hydrogen or together represent oxo. Examples of Cy^1 include azetidiny, pyrrolidinyl, piperidinyl, azepinyl, morpholinyl, thiamorpholinyl, piperazinyl, imidazolidinyl, pyrazolyl, imidazolyl, in which the ring is optionally substituted as provided above.

In another subset of formula I are compounds of formula Id:



Id

wherein Cy^2 is a 3- to 7-membered non-aromatic ring containing $N-R^f$, and optionally containing an additional heteroatom selected from O, $S(O)_m$ and $N-R^f$, and said ring being optionally substituted with 1 to 3 groups selected from oxo and R^d . In one embodiment of formula Id, Cy^2 is a 4- to 6-membered non-aromatic ring containing $N-R^f$, and optionally containing an additional heteroatom selected from O, $S(O)_m$ and $N-R^f$, and said ring being optionally substituted with 1 to 3 groups selected from oxo and R^d . In another embodiment of formula Id, X is a bond. In yet another embodiment of formula Id R^2 and R^3 are each hydrogen, or taken together is oxo. Examples of Cy^2 include 2- and 3-azetidiny, 2- and 3-pyrrolidinyl, 2-, 3- and 4-piperidinyl, 2-, 3- and 4-azepinyl, 2- and 3-morpholinyl, 2- and 3-thiamorpholinyl, 2- and 3-piperazinyl, 2-, 4- and 5-imidazolidinyl in which the nitrogen of each named ring is an $N-R^f$ group, and each ring is optionally substituted as provided above.

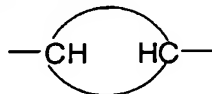
As used herein, unless otherwise defined or limited, the following definitions apply:

"Alkyl" includes straight or branched carbon chains of the designated length. Exemplary of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tertiary butyl, pentyl, isopentyl, hexyl, isohexyl, and the like.

5 "Alkenyl" includes straight and branched carbon chains of the designated length having at least one carbon-carbon double bond. Examples of alkenyl group include vinyl, allyl, 1-propenyl, 2-propenyl, isobutylene, hexadienyl, octenyl, and the like.

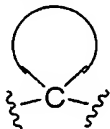
10 "Alkynyl" includes straight and branched carbon chains of the designated length having at least one carbon-carbon triple bond. Examples of alkynyl group include ethynyl, propargyl, 1-butyne, 2-butyne, 3-butyne, 4-pentyne, and the like.

The term "cycloalkylene" is a carbocyclic ring with the designated number of ring carbon atoms represented as:



15 Non-limiting examples of cycloalkylene include 1,2-cyclopropyl, 1,3-cyclobutyl, 1,3-cyclopentyl, 1,4-cyclohexyl, and the like.

The term "cycloalkylidene" is a carbocyclic ring with the designated number of ring carbon atoms represented as:



20 Non-limiting examples include 1,1-cyclopropylidene, 1,1-cyclobutylidene, 1,1-cyclopentylidene, 1,1-cyclohexylidene and the like.

The term "halogen" is intended to include the halogen atoms fluorine, chlorine, bromine and iodine.

25 The term "aryl" is an aromatic mono- or bicyclic carbocycle having from 6 to 10 carbon atoms, optionally fused to a 4- to 6-membered non-aromatic ring containing 0-3 heteroatoms selected from N, O and S(O)_m. Examples include phenyl methylenedioxyphenyl and naphthyl.

30 "Heteroaryl" is a mono-or bicyclic aromatic ring containing from 1 to 6 heteroatoms independently selected from N, O and S(O)_m wherein each ring has five or six ring atoms. Examples of heteroaryl include pyridyl, pyrimidinyl, pyrrolyl, furyl, thienyl, imidazolyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, oxadiazolyl, oxazolyl,

imidazolidinyl, pyrazolyl, isoxazolyl, benzothiadiazolyl, indolyl, indolinyl, benzodioxolyl, benzodioxanyl, benzothiophenyl, benzofuranyl, benzimidazolyl, benzisoxazolyl, benzothiazolyl, quinolinyl, benzotriazolyl, benzoxazolyl, purinyl, furopyridine and thienopyridine.

5 "Heterocycle" is a 3- to 7-membered non-aromatic ring containing 1-4 heteroatoms selected from N, O and S(O)_m, which may be optionally fused to a benzene ring. Examples of heterocycle include oxiranyl, aziridinyl, azetidiny, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothienyl including sulfoxide and sulfones thereof, 2,3- and 2,5-dihydrofuranyl, 1,3-dioxanyl, 1,3-dioxolanyl, 10 pyrrolidinyl, imidazoliny, imidazolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, benzoxazinyl, 2,3-dihydrobenzofuranyl 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl.

 The term "composition", as in pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) 15 that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing 20 a compound of the present invention and a pharmaceutically acceptable carrier.

 Compounds of Formula I contain one or more asymmetric centers and can thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. The present invention is meant to comprehend all such isomeric forms of the compounds of Formula I as individual 25 isomers as well as mixtures thereof.

 Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

 Some of the compounds described herein may exist with different 30 points of attachment of hydrogen, referred to as tautomers. Such an example may be a ketone and its enol form known as keto-enol tautomers. The individual tautomers as well as mixture thereof are encompassed within compounds of Formula I.

 Compounds of the Formula I may be separated into diastereoisomeric pairs of enantiomers by, for example, fractional crystallization from a suitable solvent, 35 for example methanol or ethyl acetate or a mixture thereof. The pair of enantiomers

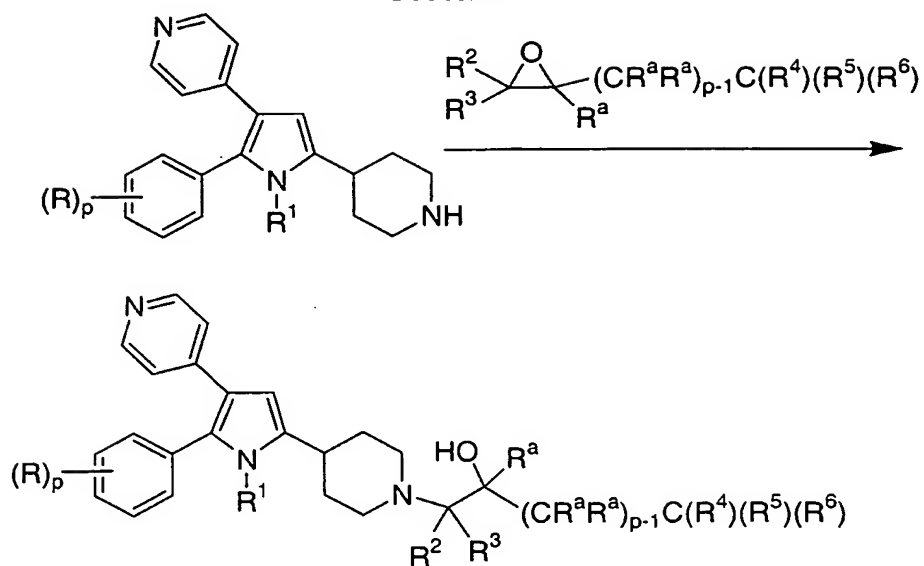
thus obtained may be separated into individual stereoisomers by conventional means, for example by the use of an optically active acid as a resolving agent. Alternatively, any enantiomer of a compound of the general Formula I may be obtained by stereospecific synthesis using optically pure starting materials or reagents of known configuration.

The term "physiologically acceptable salts" refers to salts prepared from non-toxic bases or acids that are physiologically acceptable to the host. When the compound of the present invention is acidic, salts may be prepared from physiologically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc and the like. In one embodiment the salts are selected from ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from physiologically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

When the compound of the present invention is basic, salts may be prepared from physiologically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pantoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like. In one embodiment acids are selected from citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

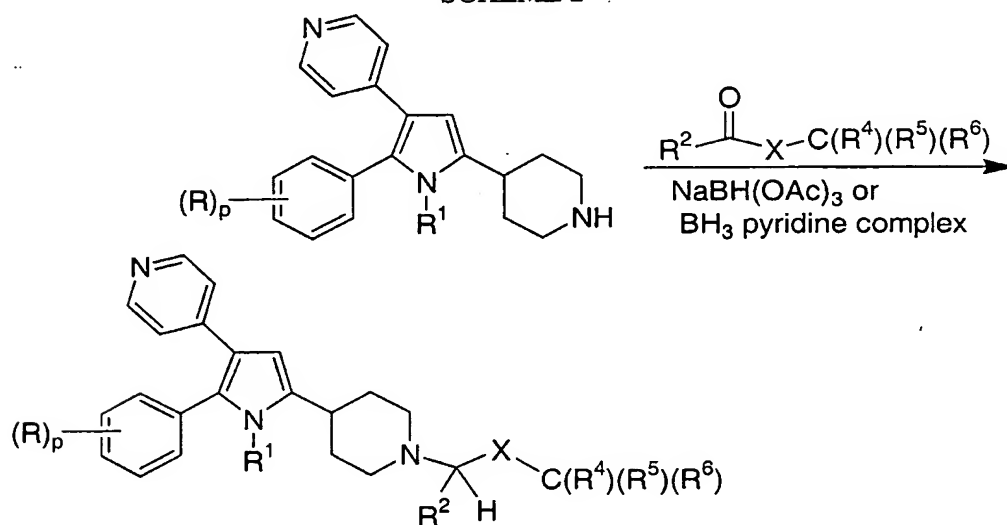
Compounds of the present invention may be prepared using a variety of organic synthesis methodologies well known in the art. Examples of suitable procedures are described in the following schemes.

SCHEME 1



In Scheme 1, the secondary amine is treated with a suitably substituted
 5 epoxide in solvents such as methanol, methanol/methylenechloride at temperatures ranging from ambient to reflux temperature to give the desired hydroxy amines.

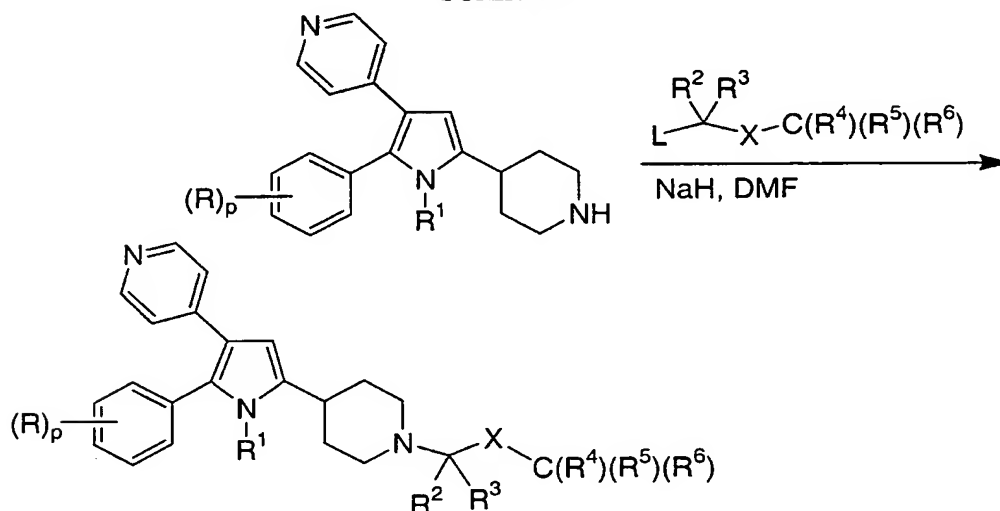
SCHEME 2



Alkylation of the piperidine nitrogen atom may be carried out by reductive amination. The reaction is carried out by treating the piperidine compound with a ketone or an aldehyde in the presence of BH_3 pyridine complex or sodium triacetoxyborohydride to give the desired alkylated piperidines.

5

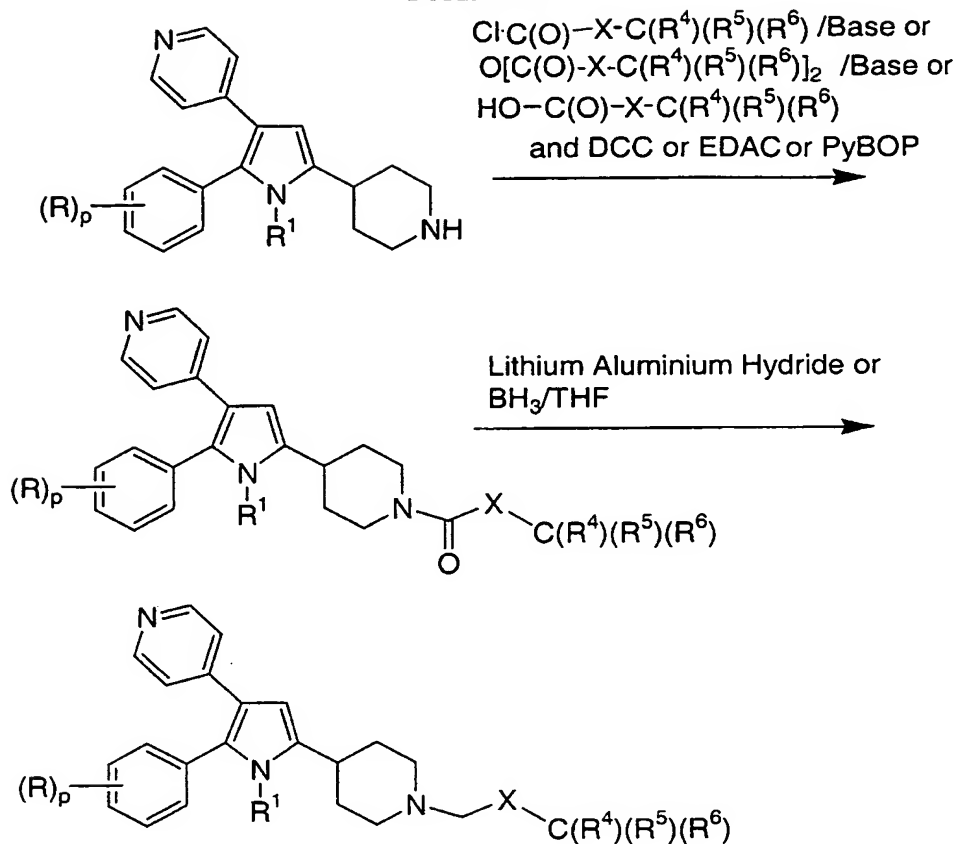
SCHEME 3



where L is a leaving group such as bromide, chloride, iodide

10 Scheme 3 depicts another method for the alkylation of the piperidine nitrogen atom. The piperidine compound is treated with a strong base such as sodium hydride in solvent such as DMF followed by alkyl halide, preferably alkyl iodide, to give the desired tertiary amines.

SCHEME 4



The acylation of the piperidine amine is depicted in Scheme 4.

- 5 Acylation may be conveniently carried out using an acylating agent such as an acid chloride, acid anhydride, or a carboxylic acid in the presence of a coupling agent such as dicyclohexylcarbodiimide. The resulting amide may be reduced using for example a borane reagent lithium aluminum hydride and the like to provide the corresponding tertiary amine.

- 10 N-oxides are prepared by treating the amine in dichloromethane with one equivalent of m-chloroperbenzoic acid, treatment with sodium bicarbonate to remove acid and final purification of N-oxide by prep TLC on silica plate eluted with NH_4OH /methanol/dichloromethane 1:9:90.

- 15 In some cases, the products from the reactions described in Schemes 1 to 4 may be further modified, for example, by the removal of protecting groups or the

further elaboration of free amino or hydroxy groups. These manipulations may include, but are not limited to, reduction, oxidation, alkylation, acylation, and hydrolysis reactions, which are commonly known to those skilled in the art.

5 Utility

The diaryl pyrroles of the present invention are useful as antiprotozoal agents. As such, they may be used in the treatment and prevention of protozoal diseases in human and animals, including poultry. Examples of protozoal diseases against which compounds of formula I may be used, and their respective causative pathogens, include: 1) amoebiasis (*Dientamoeba* sp., *Entamoeba histolytica*); 2) giardiasis (*Giardia lamblia*); 3) malaria (*Plasmodium* species including *P. vivax*, *P. falciparum*, *P. malariae* and *P. ovale*); 4) leishmaniasis (*Leishmania* species including *L. donovani*, *L. tropica*, *L. mexicana*, and *L. braziliensis*); 5) trypanosomiasis and Chagas disease (*Trypanosoma* species including *T. brucei*, *T. theileri*, *T. rhodesiense*, *T. gambiense*, *T. evansi*, *T. equiperdum*, *T. equinum*, *T. congolense*, *T. vivax* and *T. cruzi*); 6) toxoplasmosis (*Toxoplasma gondii*); 7) babesiosis (*Babesia* sp.); 8) cryptosporidiosis (*Cryptosporidium* sp.); 9) dysentery (*Balantidium coli*); 10) vaginitis (*Trichomonas* species including *T. vaginitis*, and *Tritrichomonas foetus*); 11) coccidiosis (*Eimeria* species including *E. tenella*, *E. necatrix*, *E. acervulina*, *E. maxima* and *E. brunetti*, *E. mitis*, *E. bovis*, *E. melagrammatis*, and *Isospora* sp.); 12) enterohepatitis (*Histomonas gallinarum*), and 13) infections caused by *Anaplasma* sp., *Besnoitia* sp., *Leucocytozoan* sp., *Microsporidia* sp., *Sarcocystis* sp., *Theileria* sp., and *Pneumocystis carinii*.

25 Dose Range

Compounds of formula I may be administered to a host in need of treatment in a manner similar to that used for other antiprotozoal agents; for example, they may be administered parenterally, orally, topically, or rectally. The dosage to be administered will vary according to the particular compound used, the infectious organism involved, the particular host, the severity of the disease, physical condition of the host, and the selected route of administration; the appropriate dosage can be readily determined by a person skilled in the art. For the treatment of protozoal diseases in humans, the oral dosage may range from 1 mg/kg to 1000 mg/kg; and the parenteral dosage may range from 0.5 mg/kg to 500 mg/kg. For veterinary therapeutic use, the oral dosage may range from 1 mg/kg to 1000 mg/kg; and the parenteral

dosage may range from 0.5 mg/kg to 500 mg/kg. For prophylactic use in humans, the oral dosage may range from 1 mg/kg to 1000 mg/kg; and the parenteral dosage may range from 0.5 mg/kg to 500 mg/kg. For prophylactic use in animal, the oral dosage may range from 1 mg/kg to 1000 mg/kg; and the parenteral dosage may range from 0.5 mg/kg to 500 mg/kg. For use as an anticoccidial agent, particularly in poultry, the compound is may be administered in the animals' feed or drinking water in accordance with common practice in the pountry industry and as described below.

Composition

10 The compositions of the present invention comprises a compound of formula I and an inert carrier. The compositions may be in the form of pharmaceutical compositions for human and veterinary usage, or in the form of feed composition for the control of coccidiosis in poultry.

15 The pharmaceutical compositions of the present invention comprise a compound of formula I as an active ingredient, and may also contain a physiologically acceptable carrier and optionally other therapeutic ingredients. The compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administrations, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

20 In practical use, compounds of formula I can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous).

25 In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed. For example, in the case of oral liquid preparations such as suspensions, elixirs and solutions, water, glycols, oils, alcohols, 30 flavoring agents, preservatives, coloring agents and the like may be used; or in the case of oral solid preparations such as powders, capsules and tablets, carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like may be included. Because of their ease of 35 administration, tablets and capsules represent the most advantageous oral dosage unit

form in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques. In addition to the common dosage forms set out above, compounds of formula I may also be administered by controlled release means and/or delivery devices.

5 Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient, as a powder or granules or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion or a water-in-oil liquid emulsion. Such compositions may be
10 prepared by any of the methods of pharmacy but all methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the
15 desired presentation. For example, a tablet may be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by
20 molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Desirably, each tablet contains from about 1 mg to about 500 mg of the active ingredient and each cachet or capsule contains from about 1 to about 500 mg of the active ingredient.

 Pharmaceutical compositions of the present invention suitable for
25 parenteral administration may be prepared as solutions or suspensions of these active compounds in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

30 The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against
35 the contaminating action of microorganisms such as bacteria and fungi. The carrier

can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

5 Suitable topical formulations include transdermal devices, aerosols, creams, ointments, lotions, dusting powders, and the like. These formulations may be prepared via conventional methods containing the active ingredient. To illustrate, a cream or ointment is prepared by mixing sufficient quantities of hydrophilic material and water, containing from about 5-10% by weight of the compound, in sufficient quantities to produce a cream or ointment having the desired consistency.

10 Pharmaceutical compositions suitable for rectal administration wherein the carrier is a solid may be presented as unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art, and the suppositories may be conveniently formed by admixture of the combination with the softened or melted carrier(s) followed by chilling and shaping molds.

15 It should be understood that in addition to the aforementioned carrier ingredients the pharmaceutical formulations described above may include, as appropriate, one or more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, preservatives (including anti-oxidants) and the like, and substances included for the purpose of rendering the formulation isotonic with the blood of the intended recipient.

20 For use in the management of coccidiosis in poultry, a compound of formula I may be conveniently administered as a component of a feed composition. Suitable poultry feed composition will typically contain from about 1 ppm to about 1000 ppm, or from about 0.0005% to about 0.05% percent, by weight of a compound of formula I. The optimum levels will naturally vary with the species of *Eimeria* involved, and can be readily determined by one skilled in the art.

25 In the preparation of poultry feed, a compound of formula I may be readily dispersed by mechanically mixing the same in finely ground form with the poultry feedstuff, or with an intermediate formulation (premix) that is subsequently blended with other components to prepare the final poultry feedstuff that is fed to the poultry. Typical components of poultry feedstuff include molasses, fermentation residues, corn meal, ground and rolled oats, wheat shorts and middlings, alfalfa, clover and meat scraps, together with mineral supplements such as bone meal, calcium carbonate and vitamins.

When the compound according to the present invention is used as an additive to the feed, it is typically incorporated into a "premix." The premix contains the active agent or agents as well as physiologically acceptable carriers and feedstuffs. The premix is relatively concentrated and is adapted to be diluted with other carriers, vitamin and mineral supplements, and feedstuffs to form the final animal feed.

5 Premixes which are intermediate in concentration of active agent between a first premix and the final animal feed are sometimes employed in the industry and can be used in implementing the present invention. When employing the present compound as sole active agent, a premix desirably contains the agent at a concentration of from
10 0.1 to 50.0% by weight. Preferred premixes will generally contain the present compound at a concentration of from 0.5 to 25.0%, by weight. The identity of the other components of the premix and ultimate animal feed is not critical. In final feeds, the concentration of the active agent is not critical and will depend on various factors known to those skilled in the art. Such factors include the relative potency of
15 the particular active agent and the severity of the coccidial challenge. In general, a final feed employing compound of the present invention as the sole anticoccidial will contain from about 0.0005 to about 0.05% by weight of said compound, preferably from about 0.0005 to about 0.005%.

Compositions containing a compound of formula I may also be
20 prepared in powder or liquid concentrate form. In accordance with standard veterinary formulation practice, conventional water soluble excipients, such as lactose or sucrose, may be incorporated in the powders to improve their physical properties. Thus one embodiment of suitable powders of this invention comprises 50 to 100% w/w, and for example 60 to 80% w/w of the compound and 0 to 50% w/w and for
25 example 20 to 40% w/w of conventional veterinary excipients. These powders may either be added to animal feedstuff, for example by way of an intermediate premix, or diluted in animal drinking water.

Liquid concentrates of this invention suitably contain a water-soluble compound combination and may optionally include a veterinarily acceptable water
30 miscible solvent, for example polyethylene glycol, propylene glycol, glycerol, glycerol formal or such a solvent mixed with up to 30% v/v of ethanol. The liquid concentrates may be administered to the drinking water of animals, particularly poultry.

The present invention contemplates using a compound of formula (I) as sole anticoccidial agent as well as in combination with one or more other
35 anticoccidial agents. Suitable anticoccidials for combination use include, but are not

limited to, amprolium, ethopabate, clopidol, meticlorpindol, decoquinate, dinitolmide, halofuginone, lasalocid, maduramicin, monensin, narasin, nicarbazine, chlortetracycline, oxytetracycline, robenidine, salinomycin, semduramicin, and diclazuril.

When used in combination with one or more other anticoccidial agent, the compound of formula (I) may be administered at or lower than the effective doses when used alone; for example, the final feed may contain about 0.0001 to about 0.02% by weight, or preferably from about 0.0005 to about 0.005% of a compound of formula (I). Similarly, the second anticoccidial agent in the combination may be used in an amount at or lower than those commonly used as a sole anticoccidial. The combination may be formulated into medicament for poultry use as described previously.

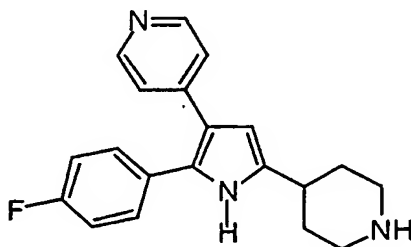
The formulated medicament may contain, in addition to anticoccidial agent(s) other therapeutic or nutritional agents commonly administered to poultry in the feed or drinking water; such other agents may be, for example, parasiticides, antibacterials, and growth promoters.

Anticoccidiosis Assay.

One-day-old White Leghorn chickens are obtained from a commercial hatchery and acclimated in a holding room. At three days of age the test animals are selected by weight, wingbanded, and randomly placed on medicated or control diets for the duration of the experiment. One or two replicates of two birds are utilized per treatment. Following 24 h premedication, in each replicate one bird is infected with *Eimeria acervulina*, the other bird is infected with *E. tenella*. Both strains of *Eimeria* are sensitive to all anticoccidial products, and have been maintained in laboratory conditions for over 25 years. The inocula consist of sporulated oocysts in tap water suspensions, administered at a dose rate of 0.25 ml per bird. The inocula levels are selected by previous dose titrations to provide a low to moderate level of infection. The *E. acervulina* portion of the experiment is terminated on Day 5, the *E. tenella* on Day 6 post infection. The measured parameters are weight gain, feed consumption and oocyst production. *E. tenella* lesion scores are also recorded for background information. Treatments which provide at least 80% reduction in oocyst production are considered active, those with 50-79% are considered partially active, and those with <50% are considered inactive. The same numerical categories in weight gain and feed consumption differentiate among treatments with good, fair or poor productivity.

REFERENCE EXAMPLE

2-(4-fluorophenyl)-5-(piperidin-4-yl)-3-(4-pyridinyl)-pyrrole



5

Step 1. 1-(4-fluorophenyl)-2-(4-pyridinyl)-ethanone

To a solution of lithium diisopropyl amide (2.0 M in heptane, tetrahydrofuran, ethyl benzene) 3.1 mL (6.3 mmol) in 6 mL of anhydrous tetrahydrofuran at -78°C under nitrogen was added 0.5 g (5.3 mmol) of 4-picoline dropwise. The reaction mixture was stirred for 20 minutes and then treated with a solution of 0.9 g (5.3 mmol) of 4-fluoro-(N-methyl-N-methoxy)-benzamide in tetrahydrofuran. The reaction mixture was warmed to 0°C and quenched by addition of 10 mL of brine. The mixture was extracted with ethyl acetate (3 x 10 mL) and the combined organic phases were dried over MgSO₄. The mixture was filtered and the filtrate was concentrated in vacuo to give the title compound as an orange solid. ¹H NMR (CDCl₃ 300 MHz): 4.23 s (d, 2H), 7.1-7.18 m (4H), 8.02 (dd, 2H), 8.55 (dd, 2H).

Step 2. 4-(1-benzyloxycarbonylpiperidin-4-yl)-2-(4-pyridyl)-1-(4-fluorophenyl)butane-1,4-dione

To a solution of the product of Step 1 (0.5 g (2.3 mmol)) in 5.0 ml of dry dimethyl sulfoxide was added 2.4 ml (2.4 mmol) of a 1M solution of sodium hexamethyldisilazide in tetrahydrofuran. After 10 minutes, a solution of 0.72 g (2.4 mmol) of the product of 4-(2-iodoacetyl)-1-(benzyloxycarbonyl)piperidine was added in 1 ml dimethyl sulfoxide dropwise. The reaction mixture was stirred for 2 hours, diluted with ethyl acetate (EtOAc, 20 ml) and washed with water (3 x 10 ml). The combined organic phases were washed with brine and dried over MgSO₄. The mixture was filtered and the filtrate was concentrated in vacuo. The residue was

purified by MPLC over silica gel eluting with 2% MeOH/CH₂Cl₂ to give the desired product. FAB ms: C₂₈H₂₇N₂O₄F:474; Observed: 475 (M⁺+1).

Step 3. 2-(4-fluorophenyl)-5-(1-benzoyloxycarbonylpiperidin-4-yl)-3-(4-pyridinyl)pyrrole

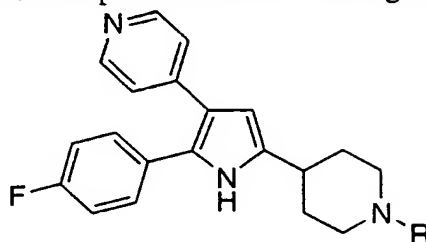
The product of Step 2 was heated in 5 ml of acetic acid in the presence of 2.0 g ammonium acetate at 110°C for 1.5 hours. The reaction mixture was diluted with ethyl acetate (10 mL) and washed with water. The combined organic phases were washed with brine and dried over MgSO₄. The mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by MPLC over silica gel eluting with 2% MeOH/CH₂Cl₂ to give the desired product. ¹H-NMR (CDCl₃, 300 MHz): 1.67 (m, 2H); 2.02 (bd, 2H); 2.75-3.0 (m, 3H); 4.29 bd, 2H); 5.12 (s, 2H); 6.19 (d, 1H); 7.03 (t, 2H); 7.18 (dd, 2H); 7.25-7.39 (m, 6H); 8.39 (dd, 2H); 8.52 (bs, 1H). FAB ms: C₂₈H₂₆N₃O₂F:455; Observed: 456 (M⁺+1).

Step 4. 2-(4-fluorophenyl)-5-(piperidin-4-yl)-3-(4-pyridinyl)pyrrole acetate salt

The product of Step 3 (183 mg) was dissolved in 5 ml of acetic acid. The solution was hydrogenated over 25 hours at atmospheric pressure in the presence of 10 mg of 10% Pd/C. The mixture was filtered and the filtrate was concentrated in vacuo to give the product. FAB ms: C₂₀H₂₀N₃F:321; Observed: 322 (M⁺+1).

The following examples are provided to more fully illustrate the invention and are not to be construed as limiting the scope of the invention in any manner. In the general procedures, reaction conditions such as temperature, time, solvent may be varied depending on the reagents used, products to be made, etc. The selection of such variables are within the skills of a person having ordinary skill in the art.

Compounds exemplified below are of the general formula



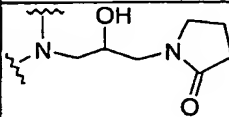
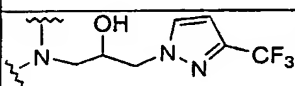
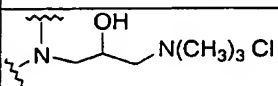
In the examples only the N-R portion is depicted. The term BOC stands for t-butyloxycarbonyl, and Fmoc stands for fluorenylmethoxycarbonyl.

- 5 NMR data are collected on a Varian XL400 spectrometer. Compounds were dissolved in CDCl_3 or CDCl_3 containing 1-2 drops of CD_3OD , unless otherwise specified.

General Procedure for Epoxide Opening

- 10 To a stirred solution of the compound of Reference Example in methanol and dichloromethane is added the appropriate epoxide. The reaction mixture is stirred at 25 to 60°C for 1-3 days, and the product is purified either by silica gel column chromatography or by preparative thin layer chromatography, eluting with 5-9% methanol, 1% NH_4OH in dichloromethane.
- 15 The following compounds were prepared in accordance with the above general procedure:

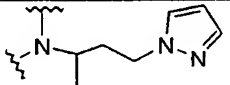
| Ex. | N-R | Epoxide | NMR |
|-----|-----|-------------------------------------|--|
| 1 | | 3-(N,N-diethylamino)propylene oxide | (CD_3OD) 1.0 (m, 6H), 1.7 (m, 2H), 2.0 (m, 2H), 2.6 (m, 6H), 2.8 (m, 3H), 3.2 (m, 2H), 3.6 (m, 2H), 3.8 (m, 1H), 6.2 (s, 1H), 7.1 (m, 2H), 7.3 (m, 2H), 7.4 (m, 2H), 8.2 (m, 2H) |
| 2 | | N-phthaloyl-3-aminopropylene oxide | 1.8-2.7 (broad m, 9H), 3.1 (broad m, 2H), 3.4-3.7 (m, 2H), 3.8 (m, 2H), 4.1 (m, 1H), 6.2 (d, $J=2.8$ Hz, 1H), |

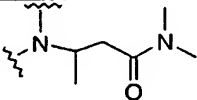
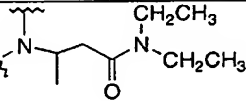
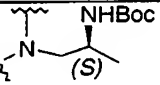
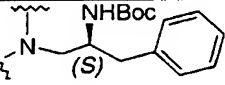
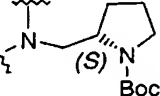
| Ex. | N-R | Epoxide | NMR |
|-----|---|---|--|
| | | | 7.0 (m, 2H), 7.2 (m, 2H), 7.3 (m, 2H), 7.7 (m, 2H), 7.8 (m, 2H), 8.2 (broad, 1H), 8.4 (m, 2H). |
| 3 |  | 3-(2-oxo-1-pyrrolidinyl)-propylene oxide | 1.02(m, 2H), 2.04(t, J=8.4Hz, 2H); 2.06(m, 1H), 2.38(t, J=8.2Hz, 2H); 3.18(m, 1H); 3.98(d, J=6.4Hz, 2H) 3.56(m, 1H), 3.92(bs, 1H). |
| 4 |  | 3-(3-trifluoromethyl-1-pyrazolyl)-propylene oxide | 2.45(m, 2H), 4.10(m, 1H), 4.21(m, 2H), 6.52(d, J=3.0Hz, 1H), 7.60(d, J=2.8Hz, 1H). |
| 5 |  | 2,3-epoxypropyl trimethylammonium chloride | 2.56(m, 2H), 3.30(s, 9H), 3.46(m, 2H), 4.44(m, 1H). |

General Procedure for Reductive Amination Using Borane

- 5 The compound of Reference Example and the appropriate carbonyl compound are dissolved in ethanol. Borane-pyridine complex is added and the reaction mixture is stirred at room temperature to about 60°C, under nitrogen atmosphere overnight. The reaction mixture is concentrated, and purified by preparative TLC eluting with 5%MeOH (10%NH₃.H₂O)/CH₂Cl₂ to give the desired product.

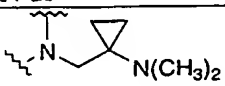
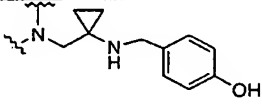
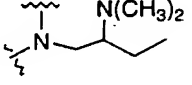
- 10 The following compounds were prepared in accordance with the above-described procedure:

| Ex. | N-R | Carbonyl | NMR |
|-----|---|----------------------------|---|
| 6 |  | 4-(1-pyrazolyl)-2-butanone | (CD ₃ OD) 2.0 (m, 5H), 2.2 (m, 1H), 2.4 (m, 1H), 2.7 (m, 3H), 3.2 (m, 2H), 4.3 (m, 2H), 6.2 (s, 1H), 6.3 (s, |

| Ex. | N-R | Carbonyl | NMR |
|-----|---|---------------------------------|--|
| | | | 1H), 7.0 (m, 2H), 7.2 (m, 2H), 7.3 (m, 2H), 7.4 (s, 1H), 7.5 (s, 1H), 8.4 (m, 2H) |
| 7 |  | N,N-dimethylaceto- acetamide | 1.2 (d, J=6.3 Hz, 3H), 2.0 (m, 4H), 2.4 (m, 1H), 2.6 (m, 2H), 2.7 (m, 1H), 2.9 (m, 1H), 2.95 (s, 3H), 3.04 (s, 2H), 3.1 (m, 2H), 3.4 (m, 1H), 6.2 (s, 1H), 7.0 (m, 2H), 7.2 (m, 2H), 7.3 (m, 2H), 8.4 (m, 2H), 8.7 (broad, 1H) |
| 8 |  | N,N-diethylaceto- acetamide | 1.2 (m, 6H), 2.0 (m, 4H), 2.4 (m, 1H), 2.6 (m, 2H), 2.7 (m, 1H), 2.9 (m, 1H), 3.1 (m, 2H), 3.4 (m, 4H), 3.5 (m, 1H), 6.2 (s, 1H), 7.0 (m, 2H), 7.2 (m, 2H), 7.3 (m, 2H), 8.4 (m, 2H), 8.8 (broad, 1H) |
| 9 |  | N-Boc-L-alaninal | 4.78(m, 1H), 3.75(m, 1H), 2.25(m, 2H), 1.45(s, 9H), 1.17(d, J=6.53Hz, 3H); MS(M+1)=479.3 |
| 10 |  | N-Boc-L-phenylalaninal | 7.33(m, overlapping, 4H), 7.23(m, overlapping, 1H), 4.80(s, br, 1H), 4.00(m, 1H), 3.00(m, overlapping, 1H), 2.85(m, 1H), 2.30(m, 2H), 1.45(s, 9H); MS(M+1)=555.3 |
| 11 |  | N-Boc-L-prolinal | 4.05(m, 1H), 3.87(m, 1H), 2.65(m, 3H), 2.00(m, 2H), |

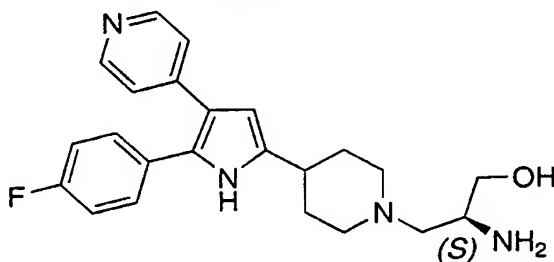
| Ex. | N-R | Carbonyl | NMR |
|-----|-----|----------|--|
| | | | 1.90(m, 2H), 1.49(s, 9H); MS(M+1)=505.3 |

Similarly, the following compounds were prepared from an amine starting material and an appropriate carbonyl compound:

| Ex | N-R | Amine | NMR |
|----|---|--------|---|
| 12 |  | Ex. 73 | 0.5(m, 2H), 0.7(m, 2H), 2.5(s, 2H). |
| 13 |  | Ex. 73 | 0.5(m, 2H), 0.7(m, 2H), 2.4(s, 2H), 3.7(s, 2H), 6.7(m, 2H), 7.1(m, 2H). |
| 14 |  | Ex. 82 | 1.0(t, J=7.4Hz, 3H), 1.4(m, 2H), 2.2(m, 1H), 2.4(s, 6H), 2.6(m, 2H). |

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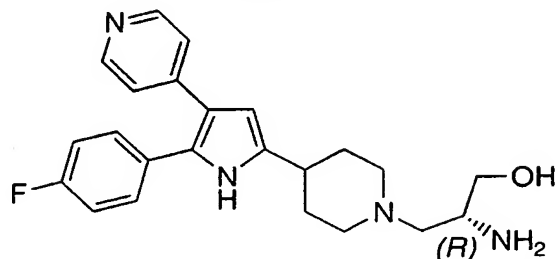
EXAMPLE 15



- 10 To a solution of the compound of Reference example (100mg, 0.31mmol) and t-butyl-(R)-(+)-4-formyl-2,2-dimethyl-3-oxazolidine carboxylate (214mg, 0.93mmol) in ethanol (15ml) under nitrogen at room temperature, borane-pyridine complex (0.12ml, 8M, 0.93mmol) was added. The resulting solution was stirred at room temperature under nitrogen overnight. The crude product was purified by flash silica gel chromatography (MeOH-CH₂Cl₂, 5:95 v/v containing 1% NH₄OH). After drying, 61mg of the title product was obtained in 25% yield. NMR

(CD₃OD) 3.78(m, 1H), 3.62(m, 1H), 3.42(m, 1H), 2.66(m, 1H), 2.57(m, 1H);
MS(M+1)=395.2

EXAMPLE 16



The title compound was obtained following the procedure described in Example 15 and using t-butyl-(S)-(+)-4-formyl-2,2-dimethyl-3-oxazolidine carboxylate as the starting material. NMR (CD₃OD) 3.57(m, 1H), 3.47(m, 1H), 3.08(m, 1H), 2.40(m, 2H); MS(M+1)=395.2

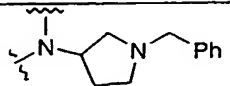
General Procedure for Reductive Amination by Triacetoxy Borohydride

To a suspension of the piperidine made in reference example, and acetic acid in anhydrous tetrahydrofuran under nitrogen at room temperature, the appropriate carbonyl compound and sodium triacetoxyborohydride are added slowly.

The resulting solution is allowed to stir at room temperature overnight. The crude product is purified by flash silica gel chromatography (MeOH-CH₂Cl₂, 8:92 v/v containing 1% NH₄OH) to provide the desired product, after drying..

The following compounds were prepared in accordance with the general procedure described above.

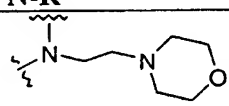
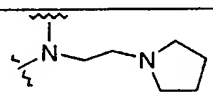
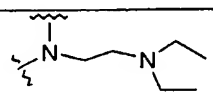
| Ex. | N-R | Carbonyl | NMR |
|-----|-----|-------------------------|---|
| 17 | | N-methyl-4-piperidinone | 8.66(s, br, 1H), 8.40(d, J=5.98Hz, 2H), 7.31(m, 2H), 7.20(d, J=6.04Hz, 2H), 7.05(m, 2H), 6.20(s, 1H), 4.74(s, 2H), 4.70(s, 1H), 3.16(m, 2H), 2.92(m, 1H), 2.10(m, 2H), 1.80(m, 4H); MS(M+1)=419.4 |

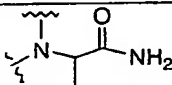
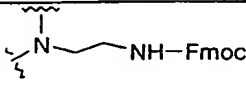
| Ex. | N-R | Carbonyl | NMR |
|-----|---|--------------------------|--|
| 18 |  | N-benzyl-3-pyrrolidinone | 9.07(s, br, 1H), 8.36(d, J=4.76Hz, 2H), 7.40~7.20(m, 7H), 7.16(d, J=5.86Hz, 2H), 7.00(m, 2H), 6.14(s, 1H), 3.63(s, 2H), 3.18(m, 1H), 3.05 (m, 2H), 2.86(m, 1H), 2.72(m, 1H), 2.63(m, 2H), 2.52(m, 1H), 2.21(m, 2H), 2.10~1.93(m, 5H), 1.87(m, 1H); MS(M+1)=481.3 |

General Procedure for N-Alkylation

To a solution of the piperidine prepared in Reference example in anhydrous N, N-dimethylformamide under nitrogen at room temperature, sodium hydride is added. The solution is stirred at room temperature for 0.5 hour and the appropriate alkyl halide is added. The resulting solution is allowed to stir at room temperature overnight. The crude product is quenched by water and extracted with ethyl acetate. The organic phase is concentrated and purified by flash column silica gel chromatography to yield the desired product.

The following compounds were prepared in accordance with the general procedure described above.

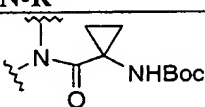
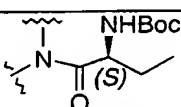
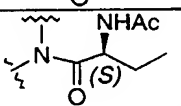
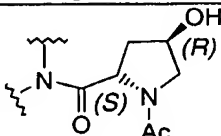
| Ex. | N-R | Alkyl halide | NMR |
|-----|---|------------------------------------|---|
| 19 |  | 4-(2-chloroethyl)-morpholine.HCl | (CD ₃ OD) 3.69(t, J=4.57Hz, 4H), 2.60(m, overlapping, 4H), 2.52(m, 4H) |
| 20 |  | 1-(2-chloroethyl)-pyrrolidine.HCl | 2.65(m, 2H), 2.55(m, overlapping, 2H), 1.80(m, 8H) |
| 21 |  | 2-bromo-N,N-diethyl-ethylamine.HBr | 2.60(m, overlapping, 6H), 2.53(m, 2H), 1.05(t, J=7.12Hz, 6H) |

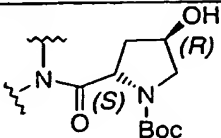
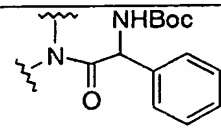
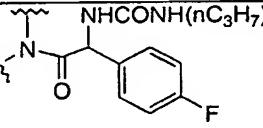
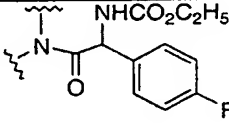
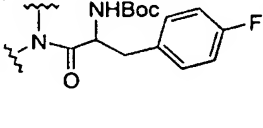
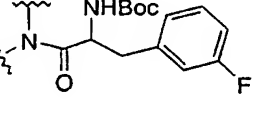
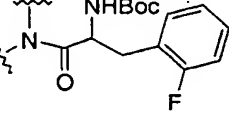
| Ex. | N-R | Alkyl halide | NMR |
|-----|---|----------------------------------|--|
| 22 |  | 2-bromo-propion- amide | (CD ₃ OD) 3.14(q, J=7.08Hz, 1H), 1.29(d, J=6.87Hz, 3H) |
| 23 |  | N-FMOC-2-amino- ethyl bromide | 7.78(d, J=7.47Hz, 2H), 7.71(d, J=7.42Hz, 2H), 7.35(m, overlapping, 4H), 4.47(t, J=7.51Hz, 2H), 4.10(t, J=7.50Hz, 1H), 3.64(t, J=8.18Hz, 2H), 2.72(d, d=7.91Hz, 2H) |

General Procedure for Amide Formation

- The appropriate carboxylic acid is suspended in CH₂Cl₂ (10mL) at ambient temperature and hydroxybenzotriazole hydrate and triethylamine and the compound of Reference example are added. Then 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) is also added. The mixture is stirred overnight and brine and CH₂Cl₂ are added. The organic layer is separated, dried and concentrated. Chromatography on Flash 40 using 9:1 methylene chloride/methanol as eluent yielded the desired amide.

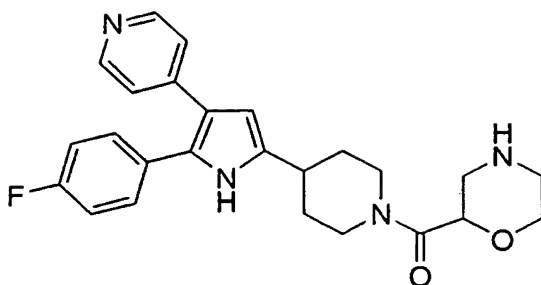
- The following compounds were prepared in accordance with the general procedure described above.

| Ex. | N-R | Carboxylic Acid | NMR |
|-----|---|---|---|
| 24 |  | 1-(N-Boc-amino)- cyclopropyl- carboxylic acid | 1.2(m, 4H), 1.4(s, 9H), 5.2(bs, 1H). |
| 25 |  | N-Boc-L-2-amino- butyric acid | 0.9(m, 3H), 1.6(m, 2H), 4.6(m, 1H), 5.4(m, 1H). |
| 26 |  | L-2-acetyl-amino- butyric acid | 0.9(m, 3H), 1.6(m, 2H), 2.0(s, 3H), 4.9(m, 1H), 6.5(m, 1h). |
| 27 |  | trans-1-acetyl-4- hydroxy-L-proline | 2.0(m, 2H), 3.4(m, 1H), 3.6(s, 3H), 3.7(m, 1H), 4.5(m, 1H), 4.9(m, 1H). |

| Ex. | N-R | Carboxylic Acid | NMR |
|-----|---|--|---|
| 28 |  | trans-N-Boc-4-hydroxy-L-proline | 1.3(m, 9H), 1.9(m, 2H), 3.4(m, 2H), 4.2(m, 1H), 4.7(m, 1H). |
| 29 |  | N-Boc-phenyl glycine | 1.4 (s, 9H), 1.7 (m, 2H), 2.0 (m, 2H), 2.8-3.1 (m, 3H), 3.9 (m, 1H), 4.7 (m, 1H), 5.6 (m, 1H), 6.0-6.2 (m, 2H), 7.0 (m, 2H), 7.2-7.4 (m, 9H), 8.4 (m, 2H) |
| 30 |  | N-(n-propylamino-carbonyl)-4-fluorophenylglycine | 0.9 (m, 3H), 1.5 (m, 2H), 1.8-2.2 (m, 5H), 2.8 (m, 2H), 3.1 (m, 2H), 3.9 (m, 1H), 4.7 (m, 1H), 5.8-6.2 (m, 2H), 7.0 (m, 4H), 7.2-7.4 (m, 6H), 8.4 (m, 2H) |
| 31 |  | N-(ethoxy-carbonyl)-4-fluorophenylglycine | 1.2 (t, 3H), 3.9 (m, 1H), 4.1 (m, 2H), 4.7 (m, 1H), 5.6 (m, 1H), 6.0 & 6.2 (2d, 1H) M+1: 545.3 |
| 32 |  | N-Boc-4-fluorophenylalanine | 1.4 (2s, 9H), 3.0 (m, 2H), 4.7 (m, 1H), 4.9 (m, 1H), 5.4 (dd, 1H), 6.1 & 6.2 (2d, 1H) M+1: 587.3 |
| 33 |  | N-Boc-3-fluorophenylalanine | 1.4 (2s, 9H), 3.9 (m, 1H), 4.7 (m, 1H), 4.9 (m, 1H), 5.4 (dd, 1H), 6.1 & 6.2 (2d, 1H) M+1: 587.3 |
| 34 |  | N-Boc-2-fluorophenylalanine | 1,4 (2s, 9H), 4.0 (m, 1H), 4.6(m, 1H), 5.0 (m, 1H), 5.4 (m, 1H), 6.2 (2d, 1H) M+1: 587.3 |

| Ex. | N-R | Carboxylic Acid | NMR |
|-----|-----|--|---|
| 35 | | 3-(N,N-diethylamino)propionic acid | 1.2 (2t, 6H), 2.8 (2q, 4H), 3.2 (m, 1H), 4.0 (m, 1H), 4.7 (m, 1H), 6.2 (d, 1H) M+1: 449.5 |
| 36 | | 3-(N-piperidinyl)propionic acid | 2.9 (m, 1H), 3.1 (m, 1H), 4.0 (m, 1H), 4.7 (m, 1H), 6.2 (d, 1H) M+1: 461.5 |
| 37 | | 3-(N-Boc-amino)propionic acid | 3.2 (m, 1H), 3.4 (m, 2H), 4.0 (m, 1H), 4.7 (m, 1H), 6.2 (d, 1H) M+1: 493.5 |
| 38 | | N-Boc-4-fluorophenylglycine | 1.4 (s, 9H), 3.2 (m, 1H), 4.0 (m, 1H), 4.6 (m, 1H), 5.9-6.2 (m, 3H) M+1: 573.5 |
| 39 | | N-(methylamino-carbonyl)-4-fluorophenylglycine | 2.7 (m, 3H), 3.9 (m, 1H), 4.7 (m, 1H), 4.9 (m, 1H), 5.8 (m, 1H), 6.0 & 6.2 (2d, 1H) M+1: 530.2 |
| 40 | | 4-(N,N-dimethylamino)butyric acid | 2.3 (s, 6H), 2.4 (2t, 4H), 2.7 (m, 1H), 2.9 (m, 1H), 3.2 (m, 1H), 4.0 (m, 1H), 4.7 (m, 1H), 6.2 (d, 1H) M+1: 435.3 |

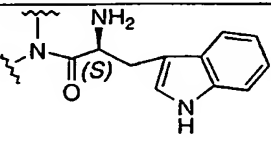
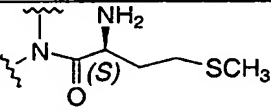
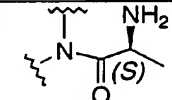
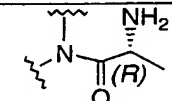
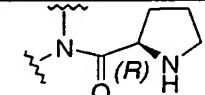
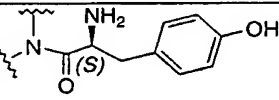
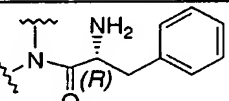
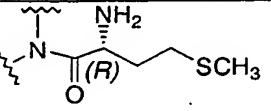
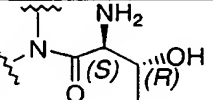
EXAMPLE 41

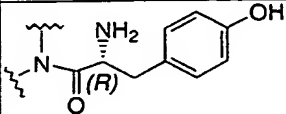
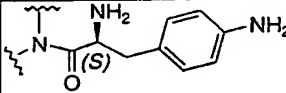
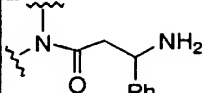
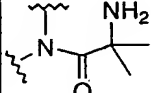


The N-Fmoc protected title compound was prepared from N-Fmoc-2-morpholinecarboxylic acid and the compound of Reference example in accordance with the general procedure for amide formation. The Fmoc-protected title compound (388mg, 0.59mmol) was dissolved in 4 mL of 10% piperidine in DMF. After stirring for one hour, solvent was evaporated *in vacuo*. Purification by preparative TLC afforded the title compound (220mg, 86%). NMR 2.8(m, 4H), 3.6(m, 1H), 3.9(m, 1H), 4.4(m, 1H).

The following compounds were prepared from the compound of Reference example and the appropriate N-BOC protected (except as noted) amino acid to form the corresponding N-BOC protected amide according to the procedure described above; the N-BOC protected amides were subsequently treated with trifluoroacetic acid as described later to provide the corresponding free amide.

| Ex | N-R | Carboxylic Acid | NMR |
|----|-----|--|---|
| 42 | | N-Boc-2-amino-3-(4-pyridyl)-propionic acid | 0.7-4.6(m,13 H) 6.06,6.18 (2s, pyrrole rotomer), 7.08-7.11 (m, 2H F-Ar) 7.23-7.36 (m, 6 Ar H), 8.24-8.28 (m, 2H pyr), 8.44-8.54 (m, 2H Pyr) |
| 43 | | (R)-N-Boc-4-hydroxyphenyl-glycine | 3.3(s, 2H), 4.6(s, 1H), 6.8(m, 2H), 7.1(m, 2H). |
| 44 | | (S)-N-Boc-4-amino-2-hydroxy-butyric acid | 1.7(m, 1H), 1.9(m, 1H), 2.9(m, 2H), 4.6(m, 1H). |

| Ex | N-R | Carboxylic Acid | NMR |
|----|---|-----------------------|--|
| 45 |  | N-Boc-L-tryptophan | (CD ₃ OD) 8.30(d, J=6.60Hz, 1H), 7.60(d, J=7.80Hz, 1H), 7.44(d, J=6.70Hz, 1H), 7.10(m, overlapping, 2H), 4.70(m, 2H), 2.95(m, 1H) |
| 46 |  | N-Boc-L-methionine | (CD ₃ OD) 4.60(m, 2H), 2.95(m, overlapping, 1H), 2.62(m, 2H), 2.15(s, 3H) |
| 47 |  | N-Boc-L-alanine | 2.92(m, 1H), 1.30(d, J=6.90Hz, 3H) |
| 48 |  | N-Boc-D-alanine | 2.92(m, 1H), 1.29(d, J=3.70Hz, 3H) |
| 49 |  | N-Boc-D-proline | 3.19(m, overlapping, 1H), 2.92(m, overlapping, 1H), 2.08(m, overlapping, 1H), 1.70(m, 4H) |
| 50 |  | N-Boc-L-tyrosine | (CD ₃ OD) 7.33(m, overlapping, 1H), 7.22(m, 1H), 7.08(m, overlapping, 1H), 7.07(m, 1H), 3.00(m, 1H), 2.63(m, 2H) |
| 51 |  | N-Boc-D-phenylalanine | 7.30(m, overlapping, 4H), 7.10(m, overlapping, 1H), 3.00(m, 1H), 2.64(m, 2H) |
| 52 |  | N-Boc-D-methionine | 3.94(m, 1H), 2.92(m, 1H), 2.75(m, 2H), 2.67(m, 1H), 2.14(s, 3H) |
| 53 |  | N-Boc-L-threonine | (CD ₃ OD) 3.82(m, 1H), 2.92(m, 1H), 1.20(m, 3H) |

| Ex | N-R | Carboxylic Acid | NMR |
|----|---|--|---|
| 54 |  | N-Boc-D-tyrosine | (CD ₃ OD) 7.33(m, overlapping, 1H), 7.23(m, 1H), 7.08(m, overlapping, 1H), 7.07(m, 1H), 3.00(m, 1H), 2.63(m, 2H) |
| 55 |  | N-Boc-4-amino-phenylalanine | (CD ₃ OD) 7.32(m, overlapping, 1H), 7.23(m, 1H), 6.68(m, 2H), 4.06(m, 2H), 3.05(m, 1H) |
| 56 |  | 3-(N-Boc-amino)-3-phenylpropionic acid | 3.8 (m, 1H), 4.6 (m, 2H), 6.2 (2s, 1H) M+1: 469.5 |
| 57 |  | N-CBZ-2-methyl-alanine* | (CD ₃ OD) 1.53(s, 6H) |

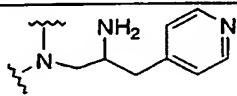
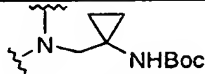
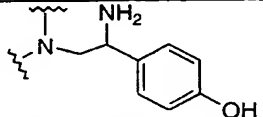
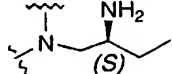
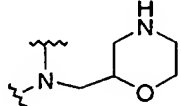
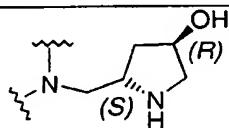
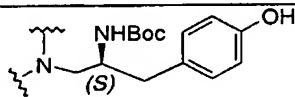
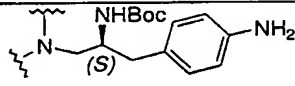
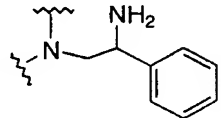
*CBZ (benzyloxycarbonyl) was removed by dissolving the compound in solvent such as methanol, treatment with a catalyst such as Pd/C, stirring under hydrogen atmosphere for 1-16 hr. followed by filtration and evaporation.

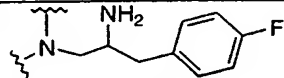
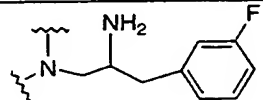
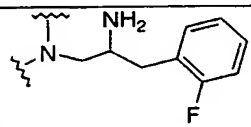
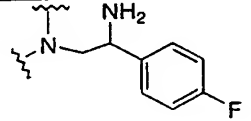
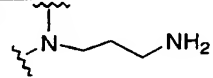
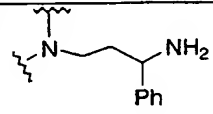
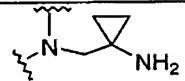
5 General Procedure for the Reduction of Amide to Amine - Borane

The amide is dissolved in tetrahydrofuran and a borane reagent such as BH₃CH₃SCH₃ or BH₃ – tetrahydrofuran is added. The mixture is stirred for 6 - 16 hours at room temperature. The reaction is quenched with methanol, and the mixture concentrated to dryness. The residue is dissolved in tetrahydrofuran, and N,N-dimethylethanolamine is added. The reaction mixture is heated under reflux for 3 hours, cooled, and evaporated to dryness. The residue is purified by preparative TLC using 90:9:1 methylene chloride/methanol/NH₄OH as eluent to give the corresponding amine.

The following compounds were prepared in accordance with the general procedure described above.

| Ex. | N-R | Amide | NMR |
|-----|-----|-------|-----|
|-----|-----|-------|-----|

| Ex. | N-R | Amide | NMR |
|-----|---|------------------------|---|
| 58 |  | Ex. 42 | 1.7-3.4 (m, 14 H), 6.17 (s, Pyrrole), 7.07-7.10 (t, J=8.9 F-Ar), 7.24(d, J=6.2 Hz Pyr), 7.32-7.35 (m, 4 H F-Ar Pyr), 8.25 (d, J=6.2 Hz Pyr) 8.43(d, J=6.2 Hz Pyr) |
| 59 |  | Ex. 24 | 0.8(bs, 2H), 1.0(bs, 2H), 1.4(s, 9H), 2.8(m, 2H). |
| 60 |  | Ex. 43 | 2.6(m, 2H), 2.5(m, 1H), 6.8(m, 2H), 7.2(m, 2H). |
| 61 |  | Ex. 101 | 1.0(t, J=7.5Hz, 3H), 1.4(m, 2H), 2.3(m, 2H), 2.9(m, 1H). |
| 62 |  | Ex. 41 | 2.4(m, 1H), 2.5(m, 2H), 2.8(m, 3H), 3.6(m, 2H), 3.8(m, 1H). |
| 63 |  | Ex. 110 | 1.4(m, 1H), 1.9(m, 1H), 2.5(m, 2H), 2.9(m, 1H), 3.2(m, 1H), 3.6(m, 1H), 4.4(m, 1H). |
| 64 |  | Ex. 50 (BOC protected) | 7.06(m, overlapping, 2H), 6.78(m, 2H), 2.83(m, 1H), 2.77(m, 1H), 2.30(m, 2H), 2.20(m, 1H), 1.45(s, 9H) |
| 65 |  | Ex. 55 (BOC protected) | (CD ₃ OD) 6.97(d, J=8.40Hz, 2H), 6.67(d, J=8.20Hz, 2H), 3.88(m, 1H), 2.60(m, 2H), 2.40(m, 2H), 1.39(s, 9H) |
| 66 |  | Ex. 104 | 2.0-2.8 (m, 9H), 3.0 (m, 1H), 3.2 (m, 1H), 4.2 (m, 1H), 6.2 (s, 1H), 7.0 (m, 2H), 7.2 (m, 2H), 7.4 (m, |

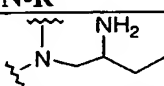
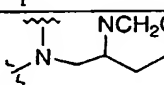
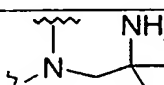
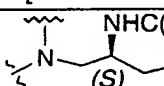
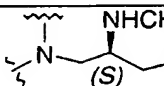
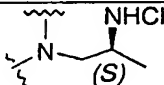
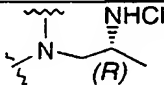
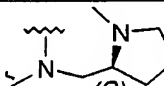
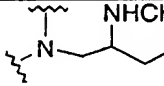
| Ex. | N-R | Amide | NMR |
|-----|---|---------|---|
| | | | 7H), 8.4 (m, 2H) |
| 67 |  | Ex. 109 | 3.3 (m, 1H), 6.2 (d, 1H) M+1: 473.3 |
| 68 |  | Ex. 115 | 3.0 (m, 2H), 3.2 (m, 1H), 6.2 (d, 1H) M+1: 473.3 |
| 69 |  | Ex. 105 | 3.0 (m, 2H), 3.3 (m, 1H), 6.2 (d, 1H) M+1: 473.3 |
| 70 |  | Ex. 107 | 3.0 (m, 1H), 3.2 (m, 1H), 4.4 (m, 1H), 6.2 (s, 1H) M+1: 459.4 |
| 71 |  | Ex. 106 | 2.5 (t, 2H), 2.6 (m, 1H), 2.8 (t, 2H), 3.1 (m, 1H), 6.2 (s, 1H) M+1: 379.4 |
| 72 |  | Ex. 56 | 3.0 (m, 2H), 4.0 (t, 1H), 6.2 (d, 1H) M+1: 455.6 |
| 73 |  | Ex. 108 | 0.5(m, 2H), 0.6(m, 2H), 2.4(s, 2H). |

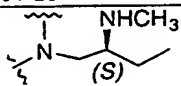
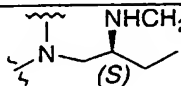
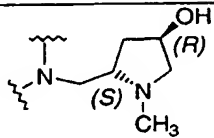
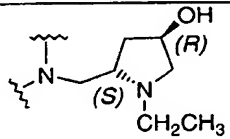
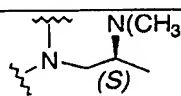
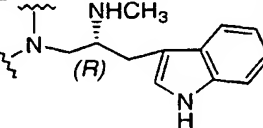
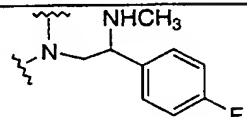
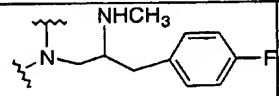
General Procedure for Lithium Aluminum Hydride Reduction

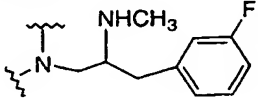
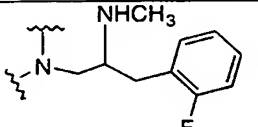
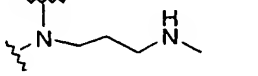
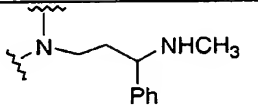
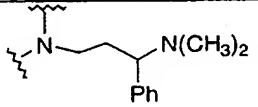
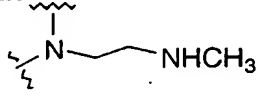
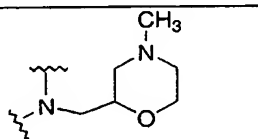
To a stirred suspension of the amide (or carbamate) in tetrahydrofuran is added equivalent amount of lithium aluminum hydride in tetrahydrofuran (1M) dropwise. After refluxing for 1 hour, the reaction is quenched with few drops of saturated sodium sulfate (or successive addition of ethyl acetate and drops of 15% NaOH, resulting precipitate filtered), and then solvent is removed *in vacuo*. Purification by silica gel chromatography afforded amino products.

The following compounds were prepared in accordance with the general procedure described above.

| Ex. | N-R | Amide/Carbamate | NMR |
|-----|-----|-----------------|-----|
|-----|-----|-----------------|-----|

| Ex. | N-R | Amide/Carbamate | NMR |
|-----|---|------------------------|---|
| 74 |  | Ex. 108 | 1.0(t, J=7.6Hz, 3H), 1.4(m, 2H), 2.5(m, 3H). |
| 75 |  | Ex. 108 (N-acetylated) | 0.9(t, J=7.4Hz, 3H), 1.2(t, J=7.2Hz, 3H), 1.4(m, 2H), 2.4m, 4H), 2.8(m, 1H). |
| 76 |  | Ex. 57 | (CD ₃ OD) 2.37(s, 2H), 1.19(s, 6H) |
| 77 |  | Ex. 10 | 8.23(s, 1H), 7.33(m, overlapping, 4H), 7.23(m, overlapping, 1H), 4.43(m, 1H), 2.90(m, 2H), 2.40(m, 2H); MS(M+1)=483.2 |
| 78 |  | Ex. 10 | 7.33(m, overlapping, 4H), 7.23(m, overlapping, 1H), 3.71(m, 1H), 2.90(m, 2H), 2.50(s, 3H), 2.20(m, 2H); MS(M+1)=469.3 |
| 79 |  | Ex. 9 | 2.74(m, 1H), 2.48(s, 3H), 2.28(m, 2H), 1.04(d, J=6.20Hz, 3H); MS(M+1)=393.2 |
| 80 |  | Epimer of Ex. 9 | (CD ₃ OD) 3.20(m, 1H), 2.62(s, 3H), 2.45(m, 2H), 1.21(d, J=6.6Hz, 3H); MS(M+1)=393.2 |
| 81 |  | Ex. 11 | 3.20(m, 1H), 2.52(s, 3H), 2.40~2.00(m, overlapping, 6H), 1.80(m, 2H); MS(M+1)=419.2 |
| 82 |  | Ex. 24 | 0.9(m, 3H), 1.1(m, 2H), 1.6(m, 1H), 2.4(m, 2H), 2.5(s, 3H). |

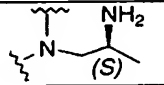
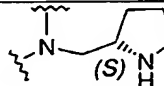
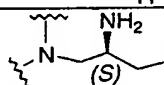
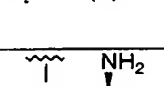
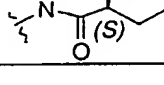
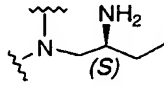
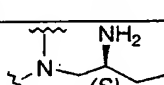
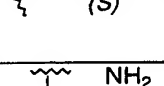
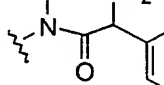
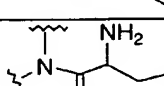
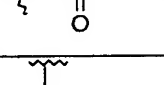
| Ex. | N-R | Amide/Carbamate | NMR |
|-----|---|--|--|
| 83 |  | Ex. 25 | 0.9(t, J=7.6Hz, 3H), 1.4(m, 2H), 2.4(m, 2H), 2.5(s, 3H), 2.6(m, 1H). |
| 84 |  | Ex. 26 | 0.9(t, J=7.4Hz, 3H), 1.2(t, J=7.2Hz, 3H), 1.4(m, 2H), 2.4m, 4H), 2.8(m, 1H). |
| 85 |  | Ex. 28 | 1.9(M, 2H), 2.3(m, 2H), 2.5(s, 3H), 2.6(m, 2H), 3.4(m, 1H), 4.3(m, 1H). |
| 86 |  | Ex. 27 | 1.1(t, J=7.3Hz, 3H), 1.8(m, 2H), 2.4(m, 2H), 2.5(m, 1H), 2.6(m, 2H), 3.1(m, 1H), 3.4(m, 1H), 4.3(m, 1H). |
| 87 |  | N-Boc-N-methyl-alanine + reference example | (CD ₃ OD) 2.50(m, 1H), 2.27(s, 6H), 2.20(m, 2H), 1.06(d, J=6.60Hz, 3H) |
| 88 |  | N-Boc-tryptophan + reference example | 8.10(s, 1H), 7.66(d, J=7.80Hz, 1H), 7.39(d, J=8.10Hz, 1H), 7.20(m, overlapping, 2H), 3.70(m, 2H), 3.05(m, 1H), 2.80(m, 1H), 2.54(s, 3H), 2.34(m, 1H) |
| 89 |  | Ex. 31 | 2.4 (s, 3H), 3.0 (m, 1H), 3.2 (m, 1H), 3.8 (m, 1H), 6.2 (m, 1H) M+1: 473.3 |
| 90 |  | Ex. 137 | 2.5 (s, 3H), 2.9 (m, 4H), 6.2 (d, 1H) M+1: 487,3 |

| Ex. | N-R | Amide/Carbamate | NMR |
|-----|---|-----------------|---|
| 91 |  | Ex. 136 | 2.5 (s, 3H), 2.9 (m, 4H), 6.2 (s, 1H) M+1: 487.3 |
| 92 |  | Ex. 138 | 2.5 (s, 3H), 2.9 (m, 4H), 6.2 (d, 1H) M+1: 487.3 |
| 93 |  | Ex. 139 | 2.5 (t, 2H), 2.6 (s, 3H), 2.7 (t, 2H), 3.1 (m, 1H), 6.2 (d, 1H) M+1: 393.4 |
| 94 |  | Ex. 142 | 3.0 (m, 1H), 3.2 (m, 1H), 3.7 (m, 1H), 6.2 (d, 1H) M+1: 469.5 |
| 95 |  | Ex. 143 | 2.4 (s, 6H), 3.0 (m, 1H), 3.2 (m, 1H), 3.5 (m, 1H), 6.2 (d, 1H) M+1: 483.3 |
| 96 |  | Ex. 23 | (CD ₃ OD) 3.72(m, 2H), 1.87(m, 1H), 1.28(m, 3H); MS(M+1)=379.2 |
| 97 |  | Ex. 123 | 1.8(m, 2H), 2.1(m, 1H), 2.3(s, 3H), 2.4(m, 1H), 2.5(m, 1H), 2.7(m, 2H), 3.6(m, 1H), 3.8(m, 1H), 3.9(m, 1H). |

General Procedure for Removal of t-BOC Protecting Group

- The BOC protected compound is treated with 10 mL of 1:1 to 2:1 trifluoroacetic acid/methylene chloride, stirred for 2 hrs., evaporated and residue
- 5 purified by preparative TLC (methanol/methylene chloride 10/90) to yield the desired product.

The following compounds were prepared from the corresponding N-Boc-protected compounds following the general procedure described above:

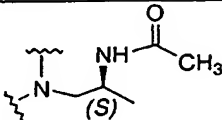
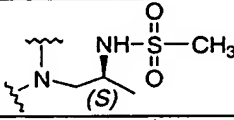
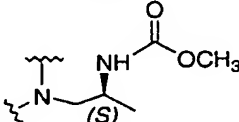
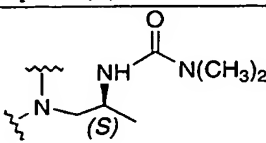
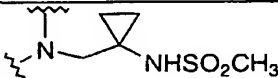
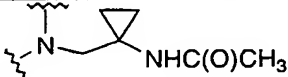
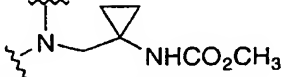
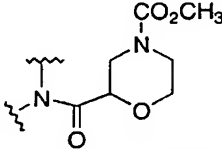
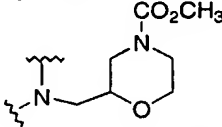
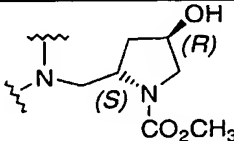
| Ex. | N-R | NMR |
|-----|---|---|
| 98 |  | (CD ₃ OD) 3.39(m, 1H), 2.40(m, overlapping, 2H), 1.23(d, J=6.59Hz, 3H); MS(M+1)=379.3 |
| 99 |  | (CD ₃ OD) 3.86(m, 1H), 3.73(m, 1H), 2.70(m, 3H), 2.05(m, 2H), 1.85(m, 2H); MS(M+1)=405.2 |
| 100 |  | 7.33(m, overlapping, 4H), 7.23(m, overlapping, 1H), 3.26(m, 1H), 2.75(m, 1H), 2.60(m, 1H), 2.30(m, 2H); MS(M+1)=455.2 |
| 101 |  | 1.0(m, 3H), 1.6(m, 2H), 3.8(m, 1H). |
| 102 |  | (CD ₃ OD) 7.06(m, overlapping, 2H), 6.71(m, 2H), 3.06(m, 1H), 2.60(m, 1H), 2.47(m, 1H), 2.30(m, overlapping, 1H), 2.00(m, overlapping, 1H) |
| 103 |  | (CD ₃ OD) 6.97(d, J=8.40Hz, 2H), 6.69(d, J=8.20Hz, 2H), 3.58(m, 1H), 2.60(m, 2H), 2.35(m, 2H) |
| 104 |  | 1.5-2.0 (m, 4H), 2.0 (m, 2H), 2.8-3.1 (m, 3H), 3.9 (m, 1H), 4.8 (m, 2H), 6.0 & 6.2 (2s, 1H), 7.0 (m, 2H), 7.2 (m, 2H), 7.4 (m, 7H), 8.4 (m, 2H) |
| 105 |  | 4.0 (m, 2H), 4.7 (m, 1H), 6.2 (2d, 1H) M+1: 487.2 |
| 106 |  | 3.2 (m, 1H), 4.0 (m, 1H), 4.7 (m, 1H), 6.2 (s, 1H) M+1: 393.4 |
| 107 |  | 3.1 (m, 1H), 3.9 (m, 1H), 4.0 4.7 (m, 1H), 5.2 (m, 1H), 6.0 & 6.2 (2d, 1H) M+1: 473.1 |
| 108 |  | 0.8(m, 2H), 1.04(m, 2H), 2.1(ds, 2H). |

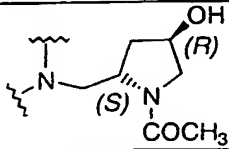
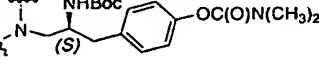
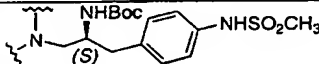
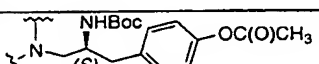
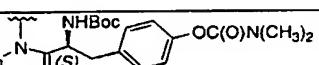
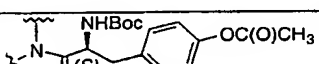
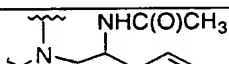
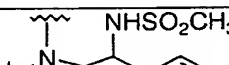
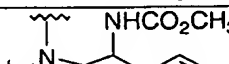
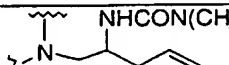
| Ex. | N-R | NMR |
|-----|-----|--|
| 109 | | 3.8 (m, 1H), 4.1 (2t, 1H) 4.7 (m, 1H), 6.1 (2s, 1H) M+1: 487.3 |
| 110 | | 1.7(m, 2H), 2.8(m, 2H), 4/3(m, 1H), 4.4(m, 1H). |
| 111 | | (CD ₃ OD) 7.24(m, 2H), 7.09(m, 2H), 3.15(m, 1H), 3.11(s, 3H), 2.98(s, 3H), 2.60(m, 2H), 2.35(m, 2H) |
| 112 | | (CD ₃ OD) 7.20(m, 4H), 3.21(m, 1H), 2.92(s, 3H), 2.70(m, 1H), 2.59(m, 1H), 2.31(m, 2H) |
| 113 | | (CD ₃ OD) 7.25(m, 2H), 7.09(m, 2H), 4.16(m, 1H), 2.90(m, 2H), 2.78(s, 3H), 2.76(s, 3H) |
| 114 | | (CD ₃ OD) 7.34(m, 2H), 7.04(m, 2H), 4.13(m, 1H), 2.94(m, 2H), 2.26(s, 3H), |
| 115 | | 3.8 (m, 1H), 4.1 (m, 1H), 4.7 & 5.2 (m, 2H), 6.1 (2s, 1H) M+1: 487.3 |

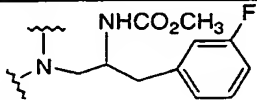
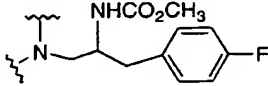
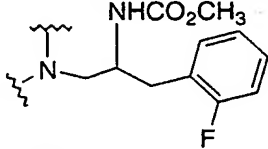
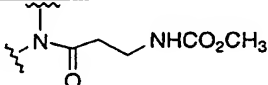
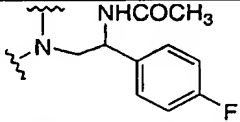
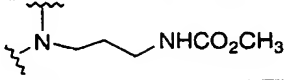
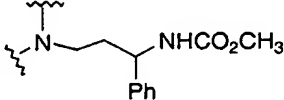
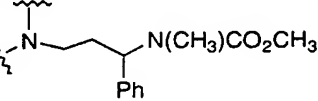
General Procedures for O- and N-Acylation

To a solution of an amine (or an alcohol) and a base such as pyridine or triethylamine in anhydrous dichloromethane under nitrogen at room temperature, an appropriate acylating agent is added. The resulting solution is stirred at room temperature for 4 hours. The crude product is purified by prep TLC (MeOH-CH₂Cl₂, 5:95 v/v containing 1% NH₄OH). After drying, the desired acylated product is obtained. Acylating agents used are acetic anhydride, methanesulfonyl chloride, methyl chloroformate or dimethylaminocarbonyl chloride.

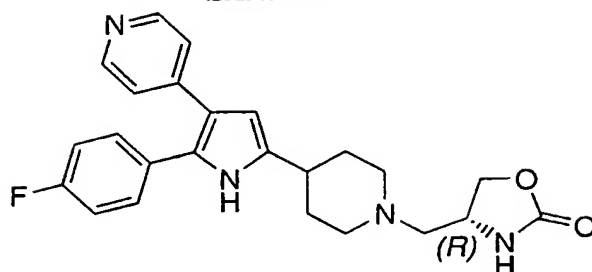
The following compounds were prepared in accordance with the general procedure described above.

| Ex. | N-R | NMR |
|-----|---|---|
| 116 |  | 5.85(s, br, 1H), 4.05(m, 1H), 2.43(m, 1H), 2.34(m, 1H), 1.99(s, 3H), 1.20(d, J=6.40Hz, 3H); MS(M+1)=421.2 |
| 117 |  | 5.40(s, br, 1H), 3.65(m, 1H), 3.03(s, 3H), 2.40(m, 2H), 1.26(d, J=6.10Hz, 3H); MS(M+1)=457.2 |
| 118 |  | 5.09(s, br, 1H), 3.86(m, 1H), 2.30(m, 2H), 1.21(d, J=6.40Hz, 3H); MS(M+1)=437.2 |
| 119 |  | 5.07(s, br, 1H), 3.82(m, 1H), 2.91(s, 6H), 2.30(m, 2H), 1.21(d, J=6.00Hz, 3H); MS(M+1)=450.2 |
| 120 |  | 0.7(m, 2H), 1.2(m, 2H), 2.6(m, 2H), 3.1(s, 3H). |
| 121 |  | 0.7(m, 2H), 1.0(m, 2H), 2.6(s, 2H), 3.5(s, 3H). |
| 122 |  | 0.7(m, 2H), 1.0(m, 2H), 2.5(s, 2H), 3.7(s, 3H). |
| 123 |  | 3.2(m, 2H), 3.8(s, 3H), 4.1(m, 5). |
| 124 |  | 2.0(m, 2H), 2.5(m, 3H), 3.1(m, 2H), 3.6(m, 1H), 3.7(s, 3H). |
| 125 |  | 2.0(m, 2H), 2.6(m, 2H), 3.2(m, 2H), 3.7(s, 3H), 4.3(m, 1H), 4.5(m, 1H). |

| Ex. | N-R | NMR |
|-----|---|---|
| 126 |  | 2.1(m, 3H), 2.2(1H), 3.0(m, 1H), 3.2(m, 2H), 3.4(m, 1H), 3.6(m, 1H), 4.4(m, 1H), 4.5(m, 1H). |
| 127 |  | (CD ₃ OD) 7.24(m, 2H), 7.00(d, J=8.20Hz, 2H), 3.95(m, 1H), 3.10(s, 3H), 2.98(s, 3H), 2.40(m, 2H), 2.08(m, 2H), 1.39(s, 9H) |
| 128 |  | (CD ₃ OD) 7.20(m, 2H), 7.09(m, 2H), 3.94(m, 1H), 2.90(s, 3H), 2.60(m, 2H), 2.45(m, 2H), 1.37(s, 9H) |
| 129 |  | (CD ₃ OD) 7.25(m, 2H), 7.00(d, J=8.40Hz, 2H), 3.95(m, 1H), 2.85(m, 1H), 2.70(m, 1H), 2.41(m, 2H), 2.25(s, 3H), 1.38(s, 9H) |
| 130 |  | (CD ₃ OD) 7.33(m, 2H), 7.08(m, 2H), 4.53(m, 1H), 2.98(m, 2H), 2.81(s, 6H), 1.42(s, 9H) |
| 131 |  | (CD ₃ OD) 7.40(m, 2H), 7.04(m, 2H), 4.53(m, 1H), 2.96(m, 2H), 2.26(s, 3H), 1.42(s, 9H) |
| 132 |  | 1.8-2.8 (m, 9H), 2.1 (s, 3H), 3.0 (m, 1H), 3.2 (m, 1H), 5.1 (m, 1H), 6.2 (d, 1H), 7.0 (m, 2H), 7.2 (m, 2H), 7.4 (m, 7H), 8.4 (m, 2H) |
| 133 |  | 2.0-2.8 (m, 9H), 2.6 (s, 3H), 3.0 (m, 1H), 3.4 (m, 1H), 4.7 (m, 1H), 6.2 (s, 1H), 7.0 (m, 2H), 7.2 (m, 2H), 7.4 (m, 7H), 8.4 (m, 2H) |
| 134 |  | 1.8 (m, 2H), 2.0 (m, 2H), 2.2 (m, 2H), 2.6 (m, 3H), 2.8 (m, 1H), 3.2 (m, 1H), 3.7 (s, 3H), 4.7 (m, 1H), 5.9 (broad, 1H), 6.2 (d, 1H), 7.0 (m, 2H), 7.2 (m, 2H), 7.4 (m, 7H), 8.4 (m, 2H), 8.5 (broad, 1H) |
| 135 |  | 1.8-2.2 (m, 5H), 2.3 (m, 1H), 2.6 (m, 3H), 2.9 (broad s, 6H), 3.1 (m, 1H), 4.8 (m, 1H), 5.8 (m, 1H), 6.2 (s, 1H), 7.0 (m, 2H), 7.2-7.4 (m, 9H), 8.4 (m, 2H) |

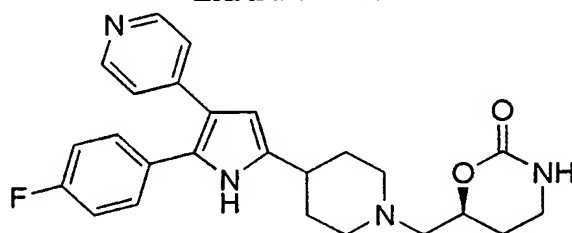
| Ex. | N-R | NMR |
|-----|---|---|
| 136 |  | 3.0 (m, 2H), 3.7 (s, 3H), 4.0 (m, 1H), 6.2 (d, 1H) M+1: 531.3 |
| 137 |  | 3.0 (m, 2H), 3.6 (s, 3H), 4.0 (m, 1H), 5.0 (m, 1H), 6.2 (d, 1H) M+1: 531.3 |
| 138 |  | 3.7 (s, 3H), 4.0 (m, 1H), 5.0 (m, 1H), 6.2 (d, 1H) M+1: 531.2 |
| 139 |  | 3.2 (m, 1H), 3.5 (m, 2H), 3.6 (s, 3H), 4.0 (m, 1H), 4.7 (m, 1H), 5.5 (m, 1H), 6.2 (d, 1H) M+1: 451.1 |
| 140 |  | 3.2 (m, 1H), 3.6 (s, 3H), 5.0 (m, 1H), 5.7 (m, 1H), 6.2 (d, 1H) M+1: 517.4 |
| 141 |  | 3.2 (t, 2H), 3.6 (s, 3H), 6.2 (s, 1H) M+1: 437.5 |
| 142 |  | 3.0 (m, 1H), 3.2 (m, 1H), 3.6 (s, 3H), 4.8 (m, 1H), 6.2 (d, 1H) M+1: 513.5 |
| 143 |  | 3.2 (m, 2H), 3.8 (s, 3H), 5.4 (m, 1H), 6.2 (d, 1H) M+1: 527.5 |

EXAMPLE 144



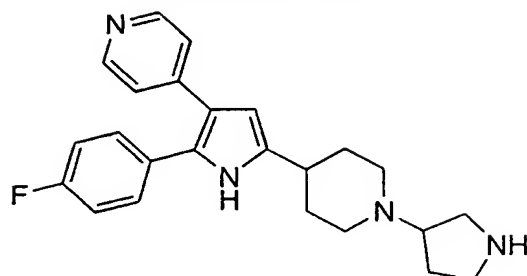
To a solution of the amine of Example 16 (46mg, 0.12mmol) and N,N-diisopropylethylamine (22ul, 0.13mmol) in anhydrous tetrahydrofuran (15ml) under nitrogen at room temperature, phosgene in toluene (66ul, 1.93M, 0.13mmol) was added. The resulting solution was stirred at room temperature for 4 hours. The crude product was purified by prep TLC (MeOH-CH₂Cl₂, 8:92 v/v containing 1% NH₄OH). After dryness, 27mg of the title product was obtained in 56% yield.

EXAMPLE 145



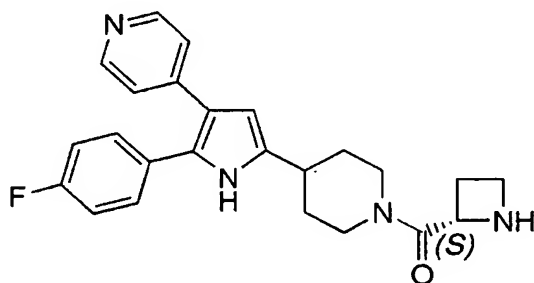
The amide of Example 44 was reduced to the corresponding amine using lithium aluminum hydride as described in the general procedure. To a stirred solution of this amine (30mg, 0.073 mmol) in 6 mL dimethylformamide was added carbonyldiimidazole (13 mg; 0.081 mmol). After stirring for 6 days, solvent was removed in vacuo. Purification by preparative TLC eluting with 8% methanol (10% NH₄OH) in dichloromethane afforded the title compound (8 mg, 25%). NMR 0.9(m, 2H), 2.6(m, 1H), 2.8(m, 1H), 3.4(m, 2H), 4.5(m, 1H), 5.2(s, 1H).

EXAMPLE 146



To a methanol solution (20ml) of the compound of Example 18
5 (250mg, 0.52mmol) was added palladium on activated carbon (10%, 25mg) and acetic
acid (glacial, 0.2ml). The resulting solution was hydrogenated at room temperature
overnight. The crude product was concentrated and purified by prep TLC (MeOH-
CH₂Cl₂, 10:90 v/v containing 1% NH₄OH). After drying, 26mg of the title product
was obtained in 13% yield. NMR (CD₃OD) 3.10(m, 2H), 3.00(m, 2H), 2.22(m,
10 overlapping, 2H), 1.80(m, 1H); MS(M+1)=391.5.

EXAMPLE 147

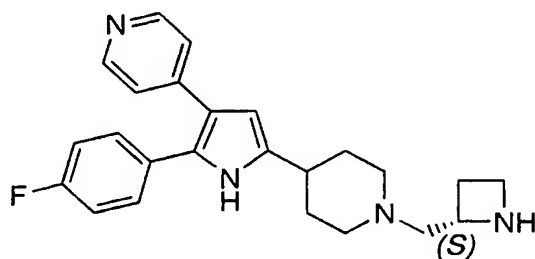


15 A solution of the compound of Reference example (2.25g), 2(S)-N-
Boc-azetidinecarboxylic acid (1.761 g, 1.25 eq), PyBOP (5.45, 1.5 eq) and
triethylamine (3.9 ml, 4 eq) in dichloromethane (40 ml) was stirred overnight at room
temperature. The reaction mixture was diluted with ethyl acetate, extracted with 1N
20 NaOH and sat NaCl, dried over Na₂SO₄ and evaporated. The product was purified by
chromatography (silica gel, ethyl acetate) to afford 2.74 g of the Boc protected product
which was deprotected by treatment with trifluoroacetic acid in dichloromethane in
the presence of anisole. NMR 400 MHz (CD₃OD) 1.60-1.75 (m, 2H), 2.0-2.2 (m,

2H), 2.32-2.48 (m, 1H)), 3.2-3.3 (m, 1H), 4.48-4.60 (m, 2 H), 6.20, 6.21 (2s, rotomer, 1H), 7.08 (m, 2H), 7.24 (m, 2 H), 7.33 (m, 2 H), 8.24 (m, 2 H).

EXAMPLE 148

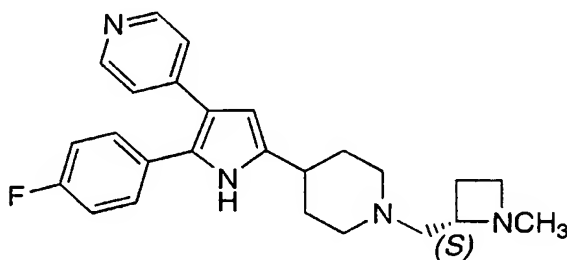
5



A solution of the compound of Example 147 (1.971 g), 1M
BH₃.tetrahydrofuran (49 ml, 10 mol) and 20 ml of tetrahydrofuran was stirred
overnight at room temperature. The excess diborane was decomposed by slow
addition of methanol at 0°C. The reaction mixture was evaporated to a small volume
and treated with N,N-dimethylethanolamine (25 ml, 50 eq) at 90° C for 4 hr,
evaporated and flushed with toluene. The product was purified by chromatography
(silica gel, CH₂Cl₂-CH₃OH-NH₄OH: 90:10:0.1) to give 1.07 g of the product.
NMR(CD₃OD) 1.70-1.81 (m, 2H), 2.36 (m, 1H)), 2.98 (d, J=7.2 Hz), 3.64 (q, J=8.2
Hz, 1H), 4.18 (m, 1H), 6.18 (s, 1H), 7.08 (m, 2H), 7.24 (m, 2 H), 7.33 (m, 2 H), 8.25
(m, 2 H).

EXAMPLE 149

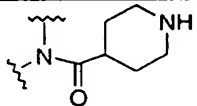
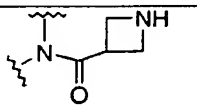
20



A mixture of the compound of Example 148 (156 mg), 37%
formaldehyde (160 ml, 5 eq), BH₃.pyridine complex (100 ml, 2 mol) and ethanol (2

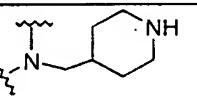
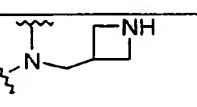
ml) was stirred overnight at r.t. The reaction mixture was treated with N,N-dimethyl-ethanolamine (2 ml) at 90° C for 2 hr, evaporated, flushed with toluene and the residue purified by prep tlc (silica gel, CH₂Cl₂- CH₃OH-NH₄OH: 90:10:0.1) to afford 140 mg of the product. NMR (CD₃OD) 1.68-1.85 (m, 2H), 2.44 (s, 3H), 6.18 (s, 1H), 7.10 (m, 2H), 7.24 (m, 2 H), 7.34 (m, 2 H), 8.25 (m, 2 H).

The procedure described in Example 147 was followed to provide the following compounds:

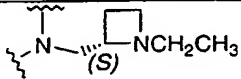
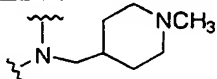
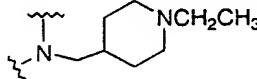

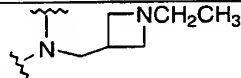
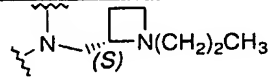
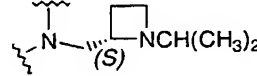
| Ex. | N-R | NMR (CD ₃ OD) |
|-----|---|---|
| 150 |  | 1.58-1.90 (m, 6 H), 2.09 (m, 2H), 4.15 (d, J=13.7 Hz, 1 H), 4.60 (d, J=12.1 Hz, 1 H) 6.20 (s, 1 H), 7.12 (m, 2H), 7.24 (m, 2 H), 7.34 (m, 2 H), 8.24 (s, 2 H). |
| 151 |  | 1.55-1.68 (m, 2H), 2.25 (d, J=12.60 Hz, 1H), 2.90 (m, 1H), 3.70 (d, J=14 Hz, 1H), 4.58 (d, J=13.3 Hz, 2 H), 6.20 (s, 1 H), 7.09 (m, 2H), 7.23 (m, 2 H), 7.33 (m, 2 H), 8.25 (m, 2 H). |

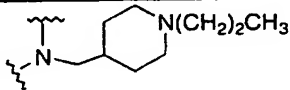
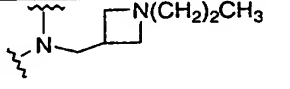
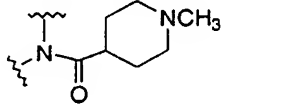
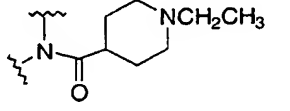
10

The procedure described in Example 148 was followed to provide the following compounds:

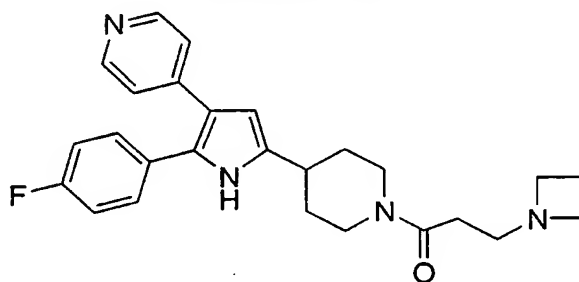
| Ex. | N-R | NMR |
|-----|---|---|
| 152 |  | 1.08-1.24 (m, 2 H), 1.63-1.82 (m, 5 H), 1.98 (d, J=12.3 Hz, 2H), 2.23 (d, J=6.6 Hz, 2 H), 3.02 (t, 4H), 6.18 (s, 1 H), 7.09 (m, 2H), 7.22 (m, 2 H), 7.34 (m, 2 H), 8.24 (m, 2 H). |
| 153 |  | 1.71-1.79 (m, 2H), 1.99 (d, J=12.6 2H), 2.16 (m, 2H), 2.61 (m, 1H), 2.67 (d, J=6.9, 2H), 2.94 (d, J=11.7 Hz, 2H), 3.8 (m, 1H), 3.54 (t, J=8 Hz, 2H) 3.80 (t, J=8 Hz, 2H), 6.18 (s, 1 H), 7.09 (m, 2H), 7.21 (m, 2 H), 7.34 (m, 2 H), 8.24 (m, 2 H). |

The procedure described in Example 149 was followed to provide the following compounds:

| Ex | N-R | NMR (CD ₃ OD) |
|-----|---|---|
| 154 |  | 1.03 (t, J=7.2 Hz, 3 H), 1.69-1.83 (m, 2H), 2.63 (m, 1H), 3.44-3.52 (m, 2H), 6.18 (s, 1H), 7.09 (m, 2H), 7.24 (m, 2 H), 7.34 (m, 2 H), 8.25 (m, 2 H). |
| 155 |  | 1.33 (m, 2 H), 1.68 (m, 1H), 1.99 (d, J=11.9 Hz, 2H), 2.14 (t, J=11.2 Hz, 2 H), 2.31 (d, J=7 Hz, 2 H), 2.40 (s, 3H), 2.63 (m, 1H), 6.18 (s, 1 H), 7.09 (m, 2H), 7.25 (m, 2 H), 7.34 (m, 2 H), 8.25 (s, 2 H) |
| 156 |  | 1.20 (t, J=7.4 Hz, 3 H), 1.32-1.42 (m, 2H), 2.32 (d, J=7.0 Hz, 2H), 2.64 (m, 1H) 2.71 (q, J=7.4 Hz, 2 H), 3.04 (d, J=11.6 Hz, 2 H), 3.20 (d, J=11.9 Hz, 2 H), 6.18 (s, 1 H), 7.09 (m, 2H), 7.24 (m, 2 H), 7.34 (m, 2 H), 8.25 (d, J=4.81 Hz, 2 H) |
| 157 |  | 1.71-1.79 (m, 2H), 1.99 (d, J=11.7 2H), 2.15 (m, 2H), 2.36 (s, 3H), 2.62 (d, J=6.9, 2H), 2.78 (m, 1H), 2.94 (d, J=11.7 Hz, 2H), 3.02 (t, J=7.7 Hz, 2H) 3.60 (t, J=8 Hz, 2H), 6.18 (s, 1 H), 7.09 (m, 2H), 7.24 (m, 2 H), 7.33 (m, 2 H), 8.25 (d, =5.2 Hz, 2 H). |
| 158 |  | 0.97 (t, J=7.1, 3H), 1.72-1.80 (m, 2H), 2.0 (d, J=11.9 Hz, 2H), 2.15 (m, 2H), 2.53 (q, J=7.1 Hz, 2H), 2.62 (d, J=6.8, 2H), 2.78 (m, 1H), 3.58 (t, J=8 Hz, 2H), 6.18 (s, 1 H), 7.09 (m, 2H), 7.24 (m, 2 H), 7.33 (m, 2 H), 8.25 (d, =5.9, Hz, 2 H). |
| 159 |  | 0.96 (t, J=7.4 Hz, 3 H), 1.43 (sext, J= 7.4 Hz, 2H), 1.68-1.82 (m, 2H), 2.61 (m, 1H), 3.41-3.43 (m, 2H), 6.18 (s, 1H), 7.09 (m, 2H), 7.24 (m, 2 H), 7.34 (m, 2 H), 8.25 (m, 2 H). |
| 160 |  | 0.97 (d, J=6.2 Hz, 3 H), 1.06 (d, J=6.2 Hz, 3 H), 1.61-1.72 (m, 2H), 3.45 (broad t, 1H), 3.55 |

| Ex | N-R | NMR (CD ₃ OD) |
|-----|--|--|
| | | (broad s, 1H), 6.18 (s, 1H), 7.09 (m, 2H), 7.24 (m, 2 H), 7.34 (m, 2 H), 8.25 (m, 2 H). |
| 161 |  | 0.93 (t, J=7.4 Hz, 3 H), 1.25-1.36 (m, 2H), 2.62 (m, 1H), 6.18 (s, 1 H), 7.09 (m, 2H), 7.25 (m, 2 H), 7.33 (m, 2 H), 8.24 (m, 2 H) |
| 162 |  | 0.91 (t, J=7.4 Hz, 3H), 1.39 (sext, J=7.4 Hz, 2H) 1.70-1.80 (m, 2H), 2.62 (d, J=6.9, 2H), 2.83 (m, 1H), 3.60 (t, J=8 Hz, 2H), 6.18 (s, 1 H), 7.10 (m, 2H), 7.24 (m, 2 H), 7.33 (m, 2 H), 8.25 (d, J=6.1, Hz, 2 H). |
| 163 |  | 2.3 (s, 3H), 3.28 (m, 1H), 4.13 (d, J=13.3 Hz, 1 H), 4.61 (d, J=13.3 Hz, 1 H) 6.21 (s, 1 H), 7.11 (m, 2H), 7.25 (m, 2 H), 7.34 (m, 2 H), 8.25 (d, J=6.1 Hz 2 H). |
| 164 |  | 1.12 (t, J=7.3 Hz, 3H), 2.45 (q, J=7.3 Hz, 2H) 3.25 (m, 1H), 4.13 (d, J=13.2 Hz, 1 H), 4.62 (d, J=13.2 Hz, 1 H) 6.21 (s, 1 H), 7.10 (m, 2H), 7.25 (m, 2 H), 7.34 (m, 2 H), 8.25 (d, J=6.1 Hz 2 H). |

EXAMPLE 165



A. 2-(4-fluorophenyl)-5-(N-acryloyl)piperidin-4-yl)-3-(4-pyridyl)pyrrole

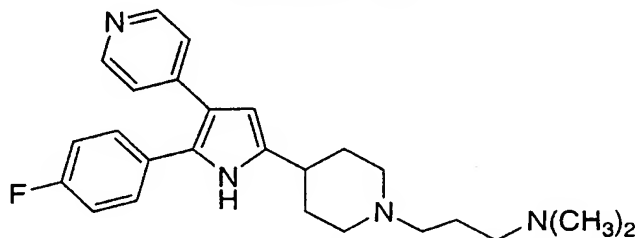
5

The general procedure for amide formation was followed using compound of Reference example and acrylic acid to provide the title compound. NMR 3.2 (m, 1H), 4.1 (m, 1H), 4.7 (m, 1H), 5.7 (dd, 1H), 6.2 (d, 1H), 6.3 (dd, 1H), 6.6 (dd, 1H)

B. 2-(4-fluorophenyl)-5-(N-(3-(1-azetidiny)propanoyl)piperidin-4-yl)-3-(4-pyridyl)pyrrole

The procedure in Step A of the next example was followed using the product of Step A above and azetidine to provide the title compound. NMR 2.1 (t, 2H), 3.2 (t, 2H), 4.0 (m, 1H), 4.7 (m, 1H), 6.2 (d, 1H)
M+1: 433.2

EXAMPLE 166



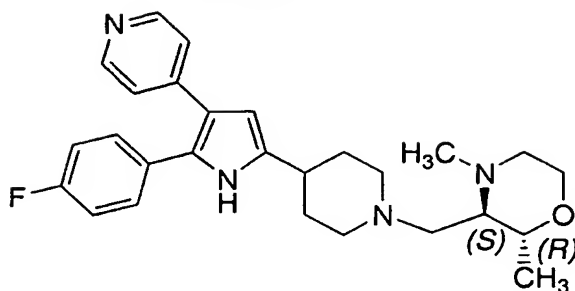
A. 2-(4-fluorophenyl)-5-(N-(2-(N,N-dimethylcarbamoyl)ethyl)piperidin-4-yl)-3-(4-pyridyl)pyrrole

To a stirred suspension of the compound of Reference example (120mg, 0.37mmol) in 10mL tetrahydrofuran and drops of methanol to clarify solution, was added dimethylacrylamide (44ul, 0.45mmol). After stirring for 3 days, solvent was removed in vacuo. Purification by prep-TLC afforded the desired amide (105mg, 67%).

B. 2-(4-fluorophenyl)-5-[N-[2-(dimethylamino)ethyl]piperidin-4-yl]-3-(4-pyridyl)pyrrole

To a stirred suspension of the amide from Step A (82mg, 0.195mmol) in 3mL tetrahydrofuran was added lithium aluminum hydride (1.0M in tetrahydrofuran, 0.39mL, 0.39mmol) dropwise. After refluxing for 3 hours, the reaction was quenched with few drops of saturated Na₂SO₄, and then solvent was removed in vacuo. Purification by silica gel chromatography afforded the title compound (71mg, 89%). NMR 1.8(m, 2H), 2.4(s, 6H), 2.4(m, 4H).

EXAMPLE 167



A. 2-(4-fluorophenyl)-5-[N-[(2S,3R)-2-(N-Boc-amino)-3-(methoxycarbonyloxy)-butyl]piperidin-4-yl]-3-(4-pyridyl)pyrrole

5 To a stirred suspension of protected 2-(4-fluorophenyl)-5-[N-[(2S,3R)-1-oxo-2-(N-Boc-amino)-3-(hydroxy)butyl]piperidin-4-yl]-3-(4-pyridyl)pyrrole (N-Boc protected compound of Ex. 53), 310mg, 0.59mmol) and NaH (59mg, 1.48 mmol) in 10 mL tetrahydrofuran at -15°C was added methyl chloroformate (67ul, 0.71mmol) dropwise. After stirring at 0°C for overnight, solvent was removed in vacuo.

10 Purification by silica gel chromatography afforded the title carbonate (140mg, 40%).

B. 2-(4-fluorophenyl)-5-[N-[(2R,3S)-(5-oxo-2-methylmorpholin-3-yl)carbonyl]-piperidin-4-yl]-3-(4-pyridyl)pyrrole

15 The product of Step A (140mg, 0.24mmol) was dissolved in 4 mL of (1:1) trifluoroacetic acid/ CH_2Cl_2 . After stirring for 2 hours, solvent was evaporated. Purification by prep-TLC afforded cyclized title compound (54mg, 50%).

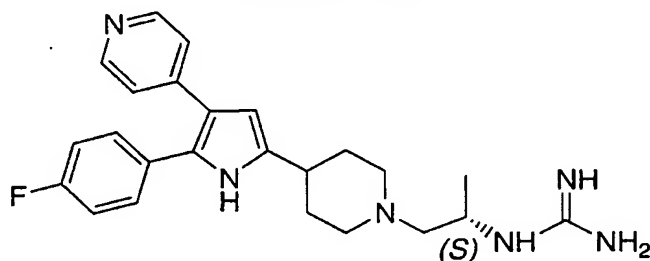
C. 2-(4-fluorophenyl)-5-[N-[(2R,3S)-(2-methylmorpholin-3-yl)methyl]piperidin-4-yl]-3-(4-pyridyl)pyrrole

20 To a stirred suspension of the product of Step B (54mg, 0.12mmol) in 2 mL tetrahydrofuran at 0°C was added lithium aluminum hydride (1.0M in tetrahydrofuran, 0.20 mL, 0.20mmol). After refluxing for 2 hours, the reaction mixture was quenched with few drops of saturated sodium sulfate, and then solvent was removed in vacuo. Purification by prep-TLC afforded the title reduction product
25 (21mg, 41%).

D. 2-(4-fluorophenyl)-5-[N-[(2R,3S)-(2,4-dimethylmorpholin-3-yl)methyl]piperidin-4-yl]-3-(4-pyridyl)pyrrole

To a stirred solution of the product of Step C (21mg, 0.048mmol) in 2mL ethanol was added formaldehyde (37% in H₂O, 20ul, 0.24mmol), followed by borane-pyridine complex (12ul, 0.097mmol). After stirring overnight, the reaction was treated with dimethylaminoethanol (1mL) and heated for 2 hours. Solvent was removed in vacuo. Purification by prep-TLC afforded the desired product (120mg, 83%). 1.2(d, J=6.3Hz, 3H), 1.9(m, 1H), 2.1(m, 2H), 2.4(s, 3H), 2.5(m, 1H), 2.7(m, 1H), 3.4(m, 1H), 3.6(m, 1H), 3.8(m, 1H).

EXAMPLE 168

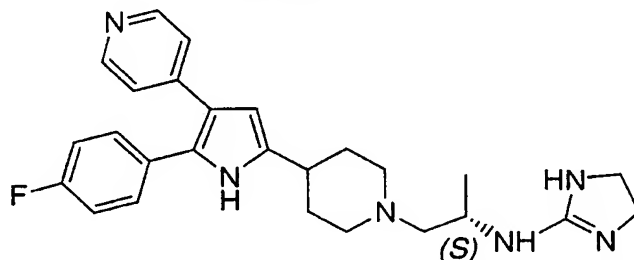


10

To a solution of the amine of Example 98 (100 mg, 0.26 mmol) in water (10 ml), 2-methyl-2-thiopseudourea sulfate (37 mg, 0.13 mmol) was added. The resulting solution was refluxed overnight. The crude product was purified by preparative TLC (MeOH-dichloromethane, 50:50 v/v containing 1% NH₄OH). After drying, 10 mg of the title product was obtained. NMR (CD₃OD) 4.00(m, 1H), 2.80(m, 2H), 1.26(d, J=6.40Hz, 3H); MS(M+1)=421.2

15

EXAMPLE 169

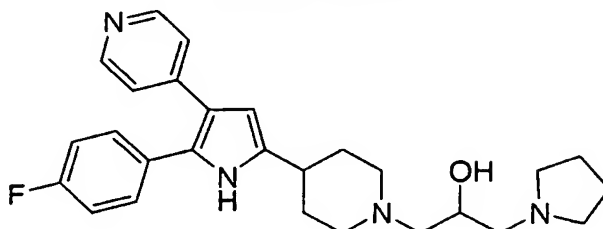


20

To a solution of the amine of Example 98 (5 mg, 0.13 mmol) in ethanol (10 ml), 2-methylthio-2-imidazoline HCl (39 mg, 0.16 mmol) was added. The resulting solution was refluxed overnight. The crude product was purified by preparative TLC (MeOH-dichloromethane, 15:85 v/v containing 1% NH₄OH). After

drying, 31 mg of the title product was obtained. NMR (CD₃OD) 3.90(m, 1H), 2.80(m, 2H), 1.28(d, J=6.40Hz, 3H); MS(M+1)=447.2

EXAMPLE 170

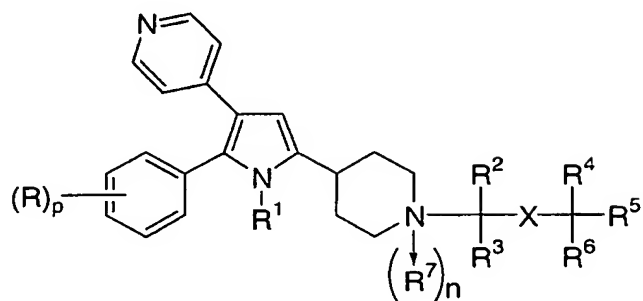


5

The title compound was obtained from the compound of Example 3 by lithium aluminum hydride reduction as described in the general procedure. NMR 1.78(m, 4H), 2.12(m, 1H), 2.32(m, 1H), 2.42(m, 3H), 2.60(m, 3H), 3.88(m, 1H).

WHAT IS CLAIMED IS:

1. A compound of formula I



I

or a physiologically acceptable salt thereof ,
wherein

n is 0 or 1;

10 m is 0, 1 or 2;

p is 1, 2 or 3;

X is (1) a bond,
(2) (CRaRa)p,
(3) C3-7 cycloalkylene, or
15 (4) C3-7 cycloalkylidene;

R is halogen

R1 is (1) hydrogen or
(2) C1-6alkyl;

R2 and R3 are independently selected from

20 (1) hydrogen,
(2) C1-6alkyl optionally substituted with ORb,
(3) C2-6alkenyl,
(4) C2-6alkynyl,
(5) phenyl optionally substituted with ORb,
25 (6) benzyl optionally substituted with ORb,
(7) CO2Rb; or

R2 and R3 together represent oxo;

when X is a bond or (CR^aR^a)_p, R² and R⁴ taken together complete a 4- to 7-membered non-aromatic ring containing N-R^f optionally substituted with 1 to 3 groups independently selected from oxo and R^d; or

- 5 when X is a bond or (CR^aR^a)_p, R² and R⁵ taken together complete a 4- to 7-membered non-aromatic ring containing 0 to 2 heteroatoms independently selected from N-R^f, O and S(O)_m, said ring being optionally substituted with 1 to 5 groups independently selected from oxo, OR^b, CH₂OR^b, and C₁₋₆alkyl;

- R⁴ is
- (1) NR^bR^b,
 - (2) NR^bC(O)R^b,
 - 10 (3) NR^bC(O)OR^b,
 - (4) NR^bC(O)NR^bR^b,
 - (5) NR^bSO₂R^b,
 - (6) NR^bC(=NR^b)NR^bR^b,
 - (7) CONR^bR^b; or
- 15 R⁴, R⁵ and the carbon atoms to which they are attached form a 3- to 7-membered non-aromatic ring containing N-R^f, optionally containing an additional heteroatom selected from O, S(O)_m and N-R^f, and said ring being optionally substituted with 1 to 3 groups selected from oxo and R^d;
- R⁵ and R⁶ are independently selected from
- 20 (1) hydrogen,
 - (2) C₁₋₁₂alkyl,
 - (3) C₂₋₁₂alkenyl,
 - (4) C₂₋₁₂alkynyl,
 - (3) C₃₋₇cycloalkyl-(C₁₋₆alkyl)_n,
 - 25 (4) heterocyclyl-(C₁₋₆alkyl)_n,
 - (5) aryl-(C₁₋₆alkyl)_n,
 - (6) heteroaryl-(C₁₋₆alkyl)_n,

- wherein alkyl, alkenyl and alkynyl are optionally substituted with 1 to 5 groups independently selected from R^c, cycloalkyl, heterocyclyl, aryl and heteroaryl are
- 30 optionally substituted with 1 to 3 groups independently selected from R^d, or R⁵, R⁶ and the carbon atoms to which they are attached form a 3- to 7-membered non-aromatic carbocyclic ring, optionally substituted with 1 to 3 groups selected from oxo and R^d; or

when X is (CR^aR^a)_p, R⁵ and any one of the R^a may together complete a 3- to 7-membered non-aromatic carbocyclic ring; or

R⁵ and R⁶ together represent oxo;

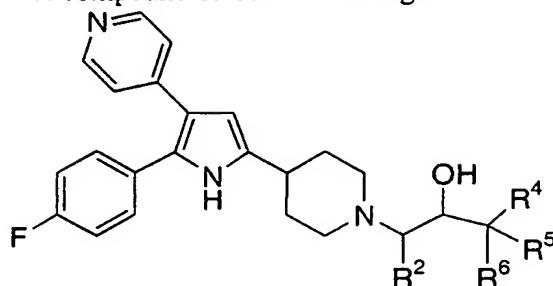
- R⁷ is
- (1) O or
 - (2) methyl;
- R^a is
- (1) hydrogen
 - (2) C₁₋₆alkyl
 - (3) OR^b;
- R^b is
- (1) a group selected from R⁵, or
- two R^b groups together with the nitrogen atom to which they are attached form a 3- to 7-membered saturated, unsaturated or aromatic ring optionally containing an additional heteroatom selected from O, S(O)_m, N and N-R^f, said ring being optionally benzo-fused and optionally substituted with 1 to 3 groups selected from oxo and R^d;
- R^c is
- (1) NReRe,
 - (2) NRgC(O)OR^e,
 - (3) NRgC(O)Re,
 - (4) NRg(C)ONReRe,
 - (5) NRgSO₂Re,
 - (6) halogen,
 - (7) S(O)_mRe,
 - (8) OR^e,
 - (9) OC(O)NReRe,
 - (10) OC(O)OR^e,
 - (11) OC(O)Re,
 - (12) OSO₂Re
 - (13) OCF₃,
 - (14) CF₃,
 - (15) C(O)OR^e,
 - (16) C(O)Re,
 - (17) oxo,
 - (18) N₃,
 - (19) CN,
 - (20) NO₂, or
 - (21) P(O)(OR^e)₂;

- R^d is
- (1) C_{1-6} alkyl optionally substituted with 1 to 5 groups selected from R^c ,
 - (2) a group selected from R^c ,
 - (3) aryl optionally substituted with 1 to 5 groups selected from R^c ,
 - 5 or
 - (4) heteroaryl optionally substituted with 1 to 5 groups selected from R^c ;
- R^e is
- (1) hydrogen,
 - (6) C_{1-12} alkyl,
 - 10 (7) C_{2-12} alkenyl,
 - (8) C_{2-12} alkynyl,
 - (3) C_{3-7} cycloalkyl- $(C_{1-6}$ alkyl) $_n$,
 - (4) aryl $(C_{1-6}$ alkyl) $_n$,
 - (9) heteroaryl $(C_{1-6}$ alkyl) $_n$,
- 15 wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heteroaryl are optionally substituted with 1 or 2 groups selected from hydroxy and C_{1-3} alkoxy; or two R^e groups together with the nitrogen atom to which they are attached form a 3- to 7-membered ring optionally containing an additional heteroatom selected from O, S or N- R_g ;
- 20 R^f is
- (1) R^e ,
 - (2) $C(O)R^e$,
 - (3) $C(O)OR^e$,
 - (4) $C(O)NR^eR^e$, or
 - (5) SO_2R^e ;
- 25 R_g is
- (1) H,
 - (2) C_{1-6} alkyl, or
 - (3) aryl $(C_{1-6}$ alkyl);

with the proviso that when R^4 is amino or t-butyloxycarbonyl amino, R^1 , R^5 and R^6 are each hydrogen, and X is a bond, then $R^2 + R^3$ is not oxo.

30

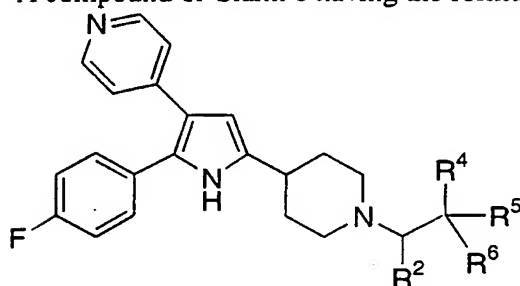
2. A compound of Claim 1 having the formula Ia:



Ia

5

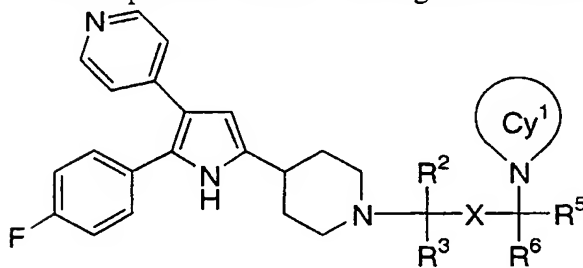
3. A compound of Claim 1 having the formula Ib:



Ib

4. A compound of Claim 3 wherein one of R⁵ or R⁶ is other than
10 hydrogen.

5. A compound of Claim 1 having the formula Ic:



Ic

- 15 wherein Cy¹ is a 3- to 7-membered saturated, unsaturated or aromatic ring optionally containing an additional heteroatom selected from O, S(O)_m, N and N-R^f, said ring

13. A compound of Claim 9 wherein R² and R³ are each hydrogen, X is a bond, and Cy² is a 4- to 6-membered non-aromatic ring containing N-R^f, and optionally containing an additional heteroatom selected from O, S(O)_m and N-R^f, and said ring being optionally substituted with 1 to 3 groups selected from oxo and OR^e.

5

14. A method for the treatment or prevention of protozoal diseases comprising administering to a host in need of such treatment a therapeutically effective amount of a compound of Claim 1.

10

15. A method for the treatment or prevention of coccidiosis in poultry comprising administering to the poultry a therapeutically effective amount of a compound of Claim 1.

15

16. A pharmaceutical composition comprising a compound of Claim 1 and an inert carrier.

20

17. A composition for the treatment or prevention of coccidiosis in poultry comprising a therapeutically effective amount of a compound of Claim 1 in poultry feedstuff.

25

18. A composition of Claim 17 wherein said second anticoccidial agent is selected from amprolium, ethopabate, clopidol, meticlorpindol, decoquinate, dinitolmide, halofuginone, lasalocid, maduramicin, monensin, narasin, nicarbazin, chlortetracycline, oxytetracycline, robenidine, salinomycin, semduramicin, and diclazuril.

30

19. A composition of Claim 17 wherein said second anticoccidial agent is selected from the group consisting of amprolium, ethopabate, lasalocid, monensin, salinomycin, and diclazuril.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/30948

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : Please See Extra Sheet.

US CL : 514/318; 546/194

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/318; 546/194

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS Online

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|-----------------------|
| A | US 5,792,778 A (DE LASZLO et al) 11 August 1998, see entire document. | 1, 2-19 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

| | |
|---|--|
| * Special categories of cited documents: | *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
| *A* document defining the general state of the art which is not considered to be of particular relevance | *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
| *E* earlier document published on or after the international filing date | *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | *G* document of the same patent family |
| *O* document referring to an oral disclosure, use, exhibition or other means | |
| *P* document published prior to the international filing date but later than the priority date claimed | |

Date of the actual completion of the international search

11 JANUARY 2001

Date of mailing of the international search report

07 MAR 2001

Name and mailing address of the ISA/US
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/30948

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 1(parts) and 2-19
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Please See Extra Sheet.
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/30948

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (7):

A61K 31/4545; C07D 401/14

BOX I. OBSERVATIONS WHERE CLAIMS WERE FOUND UNSEARCHABLE

2. Where no meaningful search could be carried out, specifically:

As the drafting of the claims is not clear and concise and encompass such an enormous amount of products, a complete search is not possible. The considerably, long list of substituents with their often numerous and/or cascading significances makes the present application not meet the requirements set forth in PCT article 6 (Claims shall be clear and concise). Therefore, the search has been based on the discernible examples set forth in the specification.